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ETHIOPIAN FOOD & DRUG AUTHORITY

# Ethiopian Food Drug Authority (EFDA)

# GOOD MANUFACTURING PRACTICE GUIDELINE FOR PHARMACEUTICAL PRODUCTS

## MAIN PRINCIPLES

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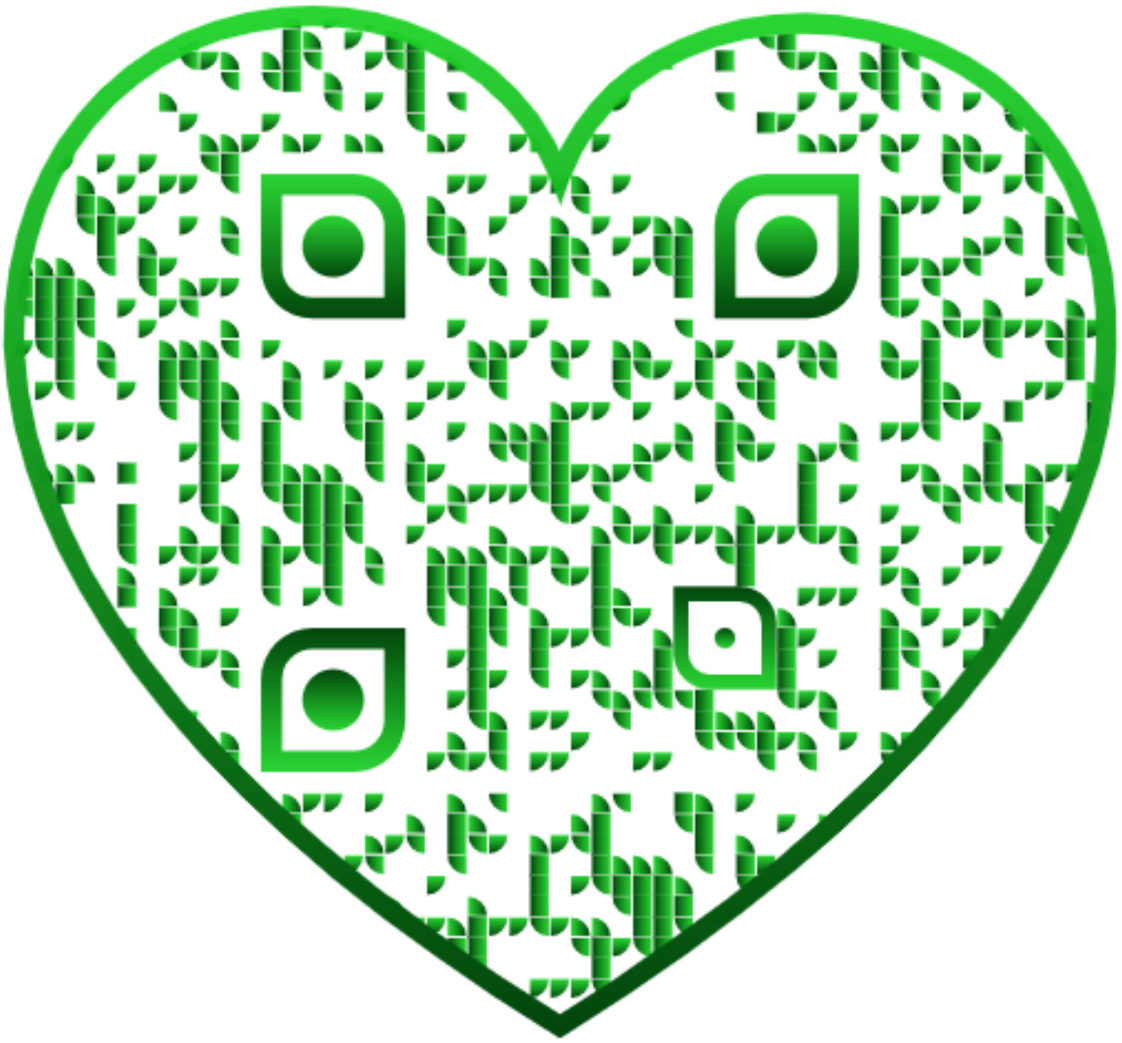
*Addis Ababa, Ethiopia*



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## ACRONYMS

| | |
|---|---|
| AC | Air Conditioner |
| AHU | Air Handling Unit |
| API | Active Pharmaceutical Ingredient |
| BMR | Batch Manufacturing Record |
| BPR | Batch Packaging Record |
| cGMP | Current Good Manufacturing Practice |
| CFU | Colony Forming Units |
| CIP | Clean In Place |
| DQ | Design Qualification |
| EU | End toxin Unit |
| FAT | Factory Acceptance Test |
| EFDA | Ethiopian Food, Drug Authority |
| FEFO | First Expire First Out |
| FIFO | First In First Out |
| GMP | Good Manufacturing Practice |
| HEPA | High Efficiency Particulate Air Filter |
| HPW | Highly Purified Water |
| HVAC | Heating, Ventilation and Air Conditioning |
| IBC | Intermediate & Bulk Container |
| INN | International Non-proprietary Name |
| IQ | Installation Qualification |
| LAF | Laminar Air Flow |
| OOS | Out of Specification |
| OQ | Operational Qualification |
| OSD | Oral Solid Dosage |
| Ph. Eur. | European Pharmacopoeia |
| Ph. Int. | International Pharmacopoeia |
| PQ | Process Qualification |
| PV | Process Validation |
| PVC | Poly Vinyl Chloride |
| PW | Purified Water |
| QA | Quality Assurance |
| QC | Quality Control |
| rDNA | Recombinant Deoxyribonucleic Acid |
| R&D | Research and Development |
| RH | Relative Humidity |

| | |
|---|---|
| RM | Raw Material |
| RO | Reverse Osmosis |
| SIP | Sterilization in Place |
| SOP | Standard Operating Procedures |
| SS | Stainless Steel |
| TOC | Total Organic Carbon |
| UDAF | Unidirectional Air Flow |
| URS | Users Requirement Specification |
| UPS | Uninterrupted Power Supply |
| USP | United States Pharmacopoeia |
| UV | Ultra Violet |
| VMP | Validation Master Plan |
| WFI | Water for Injection |
| WHO | World Health Organization |
| WPU | Water for Pharmaceutical Use |

## ACKNOWLEDGMENTS

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## INTRODUCTION

This guideline is intended to help manufacturers implementing modern quality systems and risk management approaches to meet the requirements of quality products to ensure their intended purpose and to protect the public health. The requirement in this guideline is established based on the mandate given to the Authority as stipulated in the Proclamation Number 661/2009 for the establishment of Food, Medicines and Healthcare Products in Ethiopia.

GMP ensures that quality is built into the organization and processes involved in the manufacture of the products and all those operations should be carried out strictly accordingto cGMP.

The guideline describes a comprehensive quality system model, which, if implemented, will allow manufacturers to support and sustain robust, modern quality systems that are consistent with cGMP regulations. The guideline consists of fifteen chapters and two annexes on manufacturing of sterile products and biological products. The inherent flexibility of the cGMP regulations should enable manufacturers to implement a quality system in a form thatis appropriate for their specific operations. This guideline applies mainly to manufacturers of medicinal products (finished pharmaceuticals). However, the principles given under each chapter and the general requirements can be extended to the manufactures of food, medical devices, herbal medicines, cosmetics, etc. In future, the Authority will establish, where appropriate, specific cGMP requirements as supplements to the main guide to address matters related to certain product quality requirements.

The guideline serves as a basic minimum requirement for both local pharmaceutical companies and foreign companies to be authorized for import products. It is also a reference and guidance tool to the Authority for GMP inspection and licensing of establishments. The requirement for establishment licensing is described in the guideline for establishment licensing.

The guideline is a minimum requirement and as such does not restrict any new technological development and concept, which have been validated and installed in the manufacturing of products to improve the quality assurance system. The guideline shall be regularly reviewedand revised considering the needs and technological growth in the pharmaceutical sector.

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## DEFINITIONS

For the purposes of this guideline, the following terms have the meanings hereby assigned to them. They may have different meaning in other contexts.

**Accelerated testing**
Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

**Acceptance Criteria**
Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical

procedures.

**Active Pharmaceutical Ingredient**
Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

**Actual Yield**
The quantity that is actually produced at any stage of production of a particular product from a given amount of input material.

**Ancillary Areas**
All subsidiary or subordinate areas in the plant, aimed to exist for the support of the main manufacturing and control process.

**Annual Review**
An evaluation, conducted at least annually, that assesses the quality standards of each drug product to determine the need for changes and/or assessment of overall compliance of drug product with specifications or manufacturing or control procedures

**Air-handling unit**
The air-handling unit serves to condition the air and provide the required air movement within a facility.

**Airlock**
An enclosed space with two or more doors which is interposed between two or more rooms, e.g., of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people orfor goods and/or equipment.

**Authority**
The Ethiopian Food, Medicine and Healthcare Administration and Control Authority

**Authorized person**
The person recognized by the Authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the requirements of marketing authorization.

**Batch (or lot)**
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

**Batch number (or lot number)**
A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from

which the production and distribution history can be determined.

**Batch manufacturing records**
All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

**Bulk product**
Any product that has completed all processing stages up to, but not including, final packaging.

**Calibration**
The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a traceable standard over an appropriate rangeof measurements. Limits for acceptance of the results of measuring should be established.

**Cell Bank System**
A system where by successive batches of a product are manufactured by culture in cells derived from the same master cell bank that is fully characterized for identity and absence of contamination.

**Cell Culture**
The result from the in-vitro growth of cells isolated from multi-cellular organisms.

**Clean area**
An area (room) with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

**Climatic zone**
The zones into which the world is divided based on the prevailing annual climatic conditions (See WHO TRS953, Appendix 1).

**Commissioning**
Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

**Container closure system**
The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the FPP. A packaging system is equivalent toa container closure system. Examples of container are; ampoules, glass bottles, etc.

**Consignment**
The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

**Containment**
A process or device to contain product, dust, or contaminants in one zone, preventing it from

escaping to another zone.

**Contamination**
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

**Controlled Area**
An area constructed and operated in such a way that some attempt is made to control the introduction of potential contaminant (an air supply approximating to grade D may be appropriate) and the consequences of accidental release of living organisms.

**Computerized system**
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

**Corrective Action**
Action taken to eliminate the causes of an existing discrepancy or other undesirable situation to prevent recurrence.

**Critical**
Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the finished product meets its specification.

**Critical Process Parameters**
Process parameters that must be controlled within established operating ranges to ensure that the finished product or intermediate will meet specifications for quality and purity.

**Critical Process Steps**
Process steps that must be controlled within established operating ranges to ensure that the finished product or intermediate will meet specifications for quality and purity.

**Cross-contamination**
Contamination of a starting material, intermediate product or finished product with another starting material or material during processing and/or production.

**Date of Manufacture**
A date fixed for the individual batch, indicating the completion date of manufacture.

**Design condition**
Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

**Discrepancy**
Datum or result outside of the expected range; an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend.

**Documentation**
All written procedures, instructions and records involved in the manufacture of drug products.

**Dosage form**
The form of the finished product, for example, tablet, capsule, elixir or suppository.

**Filter**
Non-shedding porous material capable of removing viable and non-viable particles from gases, air, and/or solution passing in and out of a closed vessel.

**Finished product**
A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

**Good Manufacturing Practice**
That part of quality assurance, which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

**High Efficiency Particulate Air Filter**
Retentive matrix designed to remove a defined percentage of particulate matter of a defined size.

**In-process control**
Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

**Intermediate product**
Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

**Manufacture**
All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

**Manufacturer**
A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

**Marketing Authorization**
An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy and quality.

**Master Cell Bank**
A culture of fully characterized cells filled into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability.

**Master formula**
A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including

the in-process controls.

**Master record**
A document or set of documents that serve as a basis for the batch documentation (blank batch record).

**Master Seed Lot**
A culture of a microorganism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability.

**Media fill**
Method of evaluating an aseptic process using a microbial growth medium (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

**Non-conformity**
A deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate, or not accordingto specified requirements

**Packaging**
All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

**Packaging Material**
Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any other packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be indirect contact with the product.

**Pharmaceutical product**
Any material or product intended for human use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control and this includes medicines, traditional medicine, medical device, cosmetics etc. The term 'Pharmaceutical product' is synonymous for 'medicinal products'.

**Pressure cascade**
A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

**Procedure**
Descriptions of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

**Production**
All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabeling, to completion of the finished product.

**Process Validation**
The documented evidence that the process, operated within established parameters, can perform

effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

**Qualification**
Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

**Quality Assurance**
Proactive and retrospective activities which provide confidence that requirement are fulfilled

**Quarantine**
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means while a decision is awaited on their release or rejection.

**Raw Materials**
All substances whether active or inactive that are employed in the processing of drugs although not all these substances necessarily remain in the bulk product.

**Reconciliation**
A comparison between the theoretical quantity and the actual quantity.

**Recovery**
The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery ofused materials for a separate use.

**Reprocessing**
Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications.
Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

**Retesting**
The conduct of repeating an analytical procedure on a different portion of the same sample.

**Retest date**
The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product

**Retest Period**
The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re- tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/ biological substances

known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

**Reworking**
Subjecting an in process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre- approved as part of the marketing authorization.

**Risk analysis**
Method to assess and characterize the critical parameters in the functionality of an equipment or process.

**Sampling Plan**
Description of the location, number of units and/or quantity of material that should be collected for testing and associated acceptance criteria.

**Self-Contained Area**
Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

**Shelf Life**
The time period during which a drug product and/or drug substance is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

**Simulated Product**
A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

**Specification**
Lists of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

**Standard operating procedure**
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection).

**Sterility Test**
Test performed to determine if viable microorganisms are present.

**Total Organic Carbon**
Is the amount of carbon bound in an organic compound and is often used as a non-specific indicator of water quality or cleanliness of pharmaceutical manufacturing equipment; where the source can be bacterial growth and metabolic activity of living organisms or chemicals.

**Turbulent flow**
Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

**Unidirectional airflow**
Unidirectional airflow is a rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent flow). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

**Validation**
Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

**Validation Master Plan**
VMP is a high-level document, which establishes an umbrella validation plan for the entire project, and is used as guidance by the project team for resource and technical planning (also referred to as master qualification plan).

**Working Seed Lot**
A culture of microorganism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for the master seed lots.

**Worst Case**
A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

# CHAPTER ONE-QUALITY MANAGEMENT

## Principle

Only the holder of a manufacturing authorization must manufacture pharmaceutical products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization and do not place the user at risk due to inadequate safety, quality or efficacy.

The attainment of this quality objective is the responsibility of top management and requires the participation and commitment of staff working in different departments of the company. To achieve the quality objective reliably there must be a comprehensively designed andcorrectly implemented system of Quality Assurance incorporating Good ManufacturingPractice, Quality Control and Quality Risk Management. It should be fully documented andits effectiveness monitored. All parts of the Quality Assurance systems should be adequatelyresourced with competent personnel, and suitable and sufficient premises, equipment andfacilities. There are additional legal responsibilities for the holder of the manufacturingauthorization and for the authorized person(s).

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of pharmaceutical products.

## Quality Assurance

1.1. Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

1.2. The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

a) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice ;
b) Production and control operations are clearly specified and Good Manufacturing Practice adopted;
c) Managerial responsibilities are clearly specified;
d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
e) All necessary controls on intermediate products, and any other in process controls and validations are carried out;
f) The finished product is correctly processed and checked, according to the defined procedures;
g) Medicinal products are not sold or supplied before an authorized person has certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products;

h) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

i) There is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the quality assurance system.

## Good Manufacturing Practice for Products

1.3. Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

1.4. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

a) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications and/or marketing authorization;

b) Critical steps of manufacturing processes and significant changes to the process are validated;

c) All necessary facilities for GMP are provided including:

   i. appropriately qualified and trained personnel;
   ii. adequate premises and space;
   iii. suitable equipment and services;
   iv. correct materials, containers and labels;
   v. approved procedures and instructions;

d) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

e) Operators are trained to carry out procedures correctly;

f) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

g) Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

h) The distribution (wholesaling) of the products minimizes any risk to their quality;

i) A system is available to recall any batch of product, from sale or supply;

j) Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products andto prevent re-occurrence.

## Quality Control

1.5. Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

1.6. The basic requirements of Quality Control are that:

a) Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
c) Test methods are validated;
d) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
e) The finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;
f) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
g) No batch of product is released for sale or supply prior to certification by an authorised person that it is in accordance with the requirements of the relevant authorisations;
h) Sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

## Product Quality Review

1.7. Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

a) A review of starting materials including packaging materials used in the product, especially those from new sources.
b) A review of critical in-process controls and finished product results.
c) A review of all batches that failed to meet established specification(s) and their investigation.
d) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
e) A review of all changes carried out to the processes or analytical methods.
f) A review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers.
g) A review of the results of the stability-monitoring programme and any adverse trends.
h) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.
i) A review of adequacy of any other previous product process or equipment corrective actions.
j) Review of post-marketing commitments and pharmacovigilance, where applicable.

k) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.
l) A review of any contractual arrangements to ensure that they are up to date.

1.8. The manufacturer and marketing authorisation holder should evaluate the results of this review and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

1.9. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification together with the marketing authorization holder should ensure that the quality review is performed in a timely manner and is accurate.

## Quality Risk Management

1.10. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the product. It can be applied both proactively and retrospectively. The quality risk management system should ensure that:

a) The evaluation of the risk to quality is based on scientific knowledge, experience withthe process and ultimately links to the protection of the patient and users;
b) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.
c) The general quality risk management process and integration in to the product quality can be referred in ICHQ9.

## CHAPTER TWO- SANITATION AND HYGIENE

### Principle

A high level of sanitation and hygiene should be practised in every aspect of the manufacture of pharmaceutical products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene.

### General

2.1. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

2.2. Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross- contamination and facilitate cleaning.

2.3. A high level of personal hygiene should be followed and observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

## CHAPTER THREE-PREMISES

### Principle

Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, buildup of dust or dirt and, in general, any adverse effect on the quality of products.

### General Requirement

3.1. Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4. Premises should be designed and equipped to afford maximum protection against the entry

of insects or other animals.

3.5. Steps should be taken in order to prevent the entry of unauthorized people.

3.6. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

## Production Area

3.7. In order to minimize the risk of a serious medical hazard due to cross contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms).

3.8. The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.9. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.10. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross- contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.11. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be

smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.12. Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses, which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.13. Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaningand disinfection.

3.14. Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.15. Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.16. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.17. Premises for the packaging of medicinal products should be specifically designed and laid out to avoid mix-ups or cross-contamination.

3.18. Productions areas should be well lit, particularly where visual on-line controls are carried out.

3.19. In-process controls may be carried out within the production area provided they do not carry any risk for the production.

## Storage Area

3.20. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.21. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.22. Receiving and dispatch bays should protect materials and products from the weather. Receptions areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.23. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.24. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.25. Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.26. Highly active (controlled) materials or products should be stored in safe and secure areas.

3.27. Printed packaging materials are considered critical to the conformity of the medicinal products and special attention should be paid to the safe and secure storage of these materials

## Weighing and sampling areas

A room for weighing (e.g. dispensing of materials) should be of appropriate design (for examples, see Figs A3.1 and A3.2). It is often advantageous to have several rooms associated with the weighing activity. These may include a pre-weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-weighing staging area, washing area and provision for waste removal. The HVAC system for such areas should ensure that the areas have at least the same area classification as other production areas where materials and products are exposed to the environment, logical flow of material and personnel, and an appropriate number of AHUs, as well as appropriate pressure differentials, containment, dust control, and rate of air exchange. The objective of having a booth in a weighing room is to provide dust containment and operator protection. For example, the dust generated at the weighing location should be extracted through a perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the material and product from contamination by the operator by means of the vertical airflow stream. The airflow velocity should be such that it does not disrupt the sensitivity of balances.

Fig. A3.1

Example of a weighing area

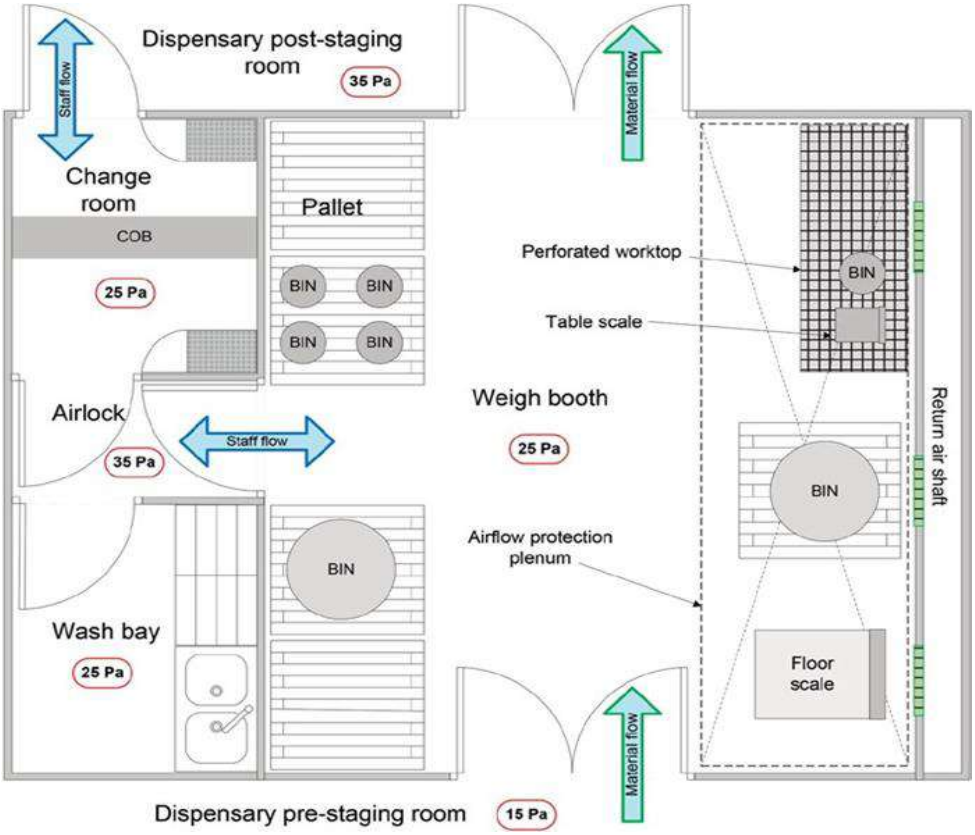



**Fig. A3.2**

**Examples of weighing areas**

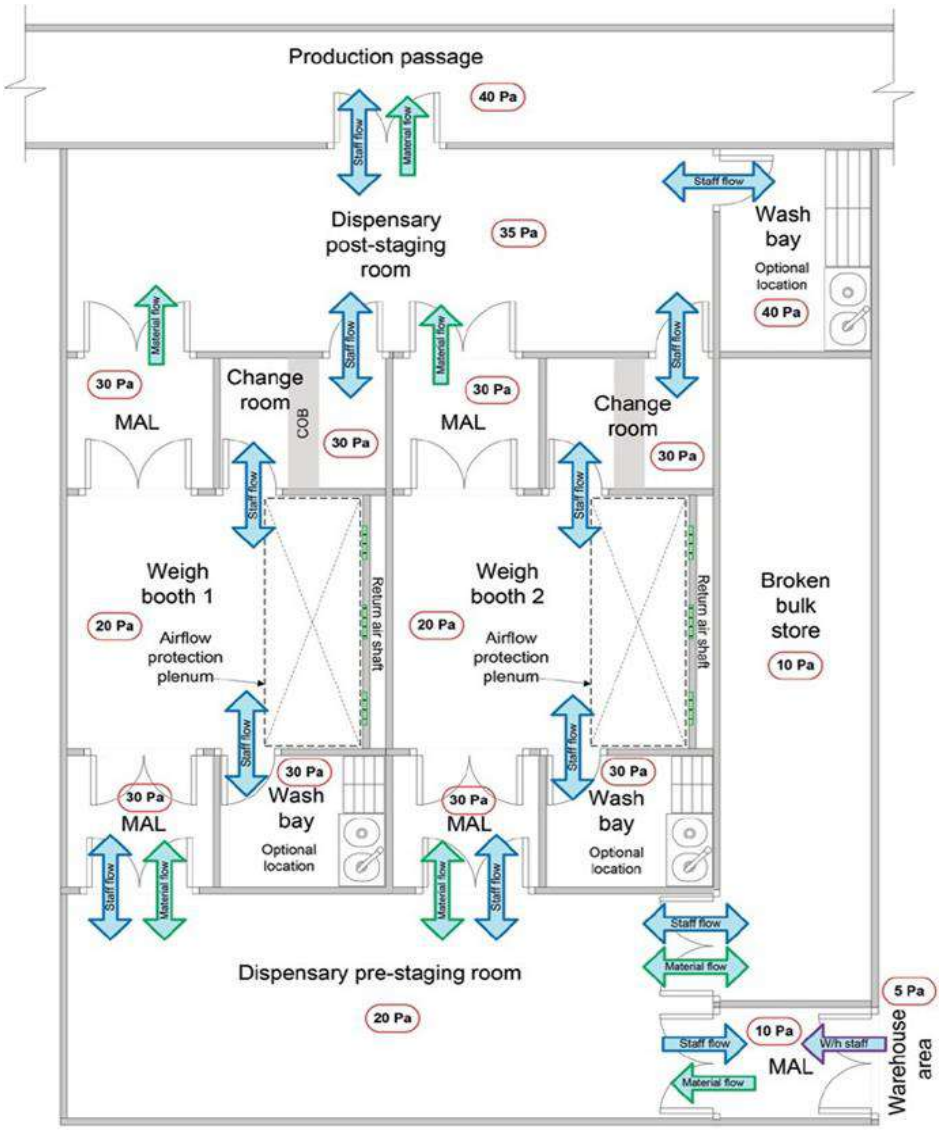
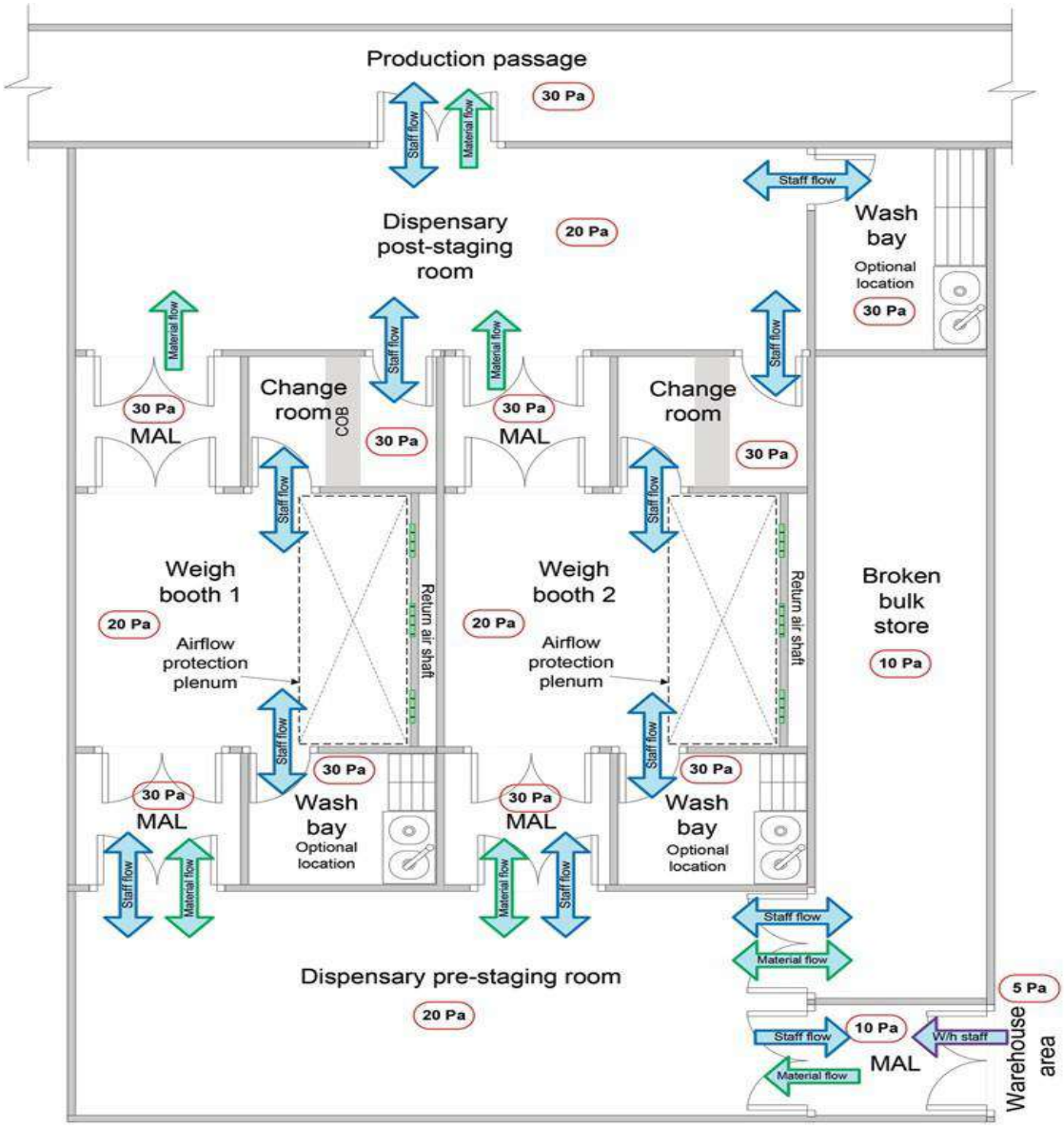

Production passage
40 Pa
Staff flow
Material flow
Dispensary post-staging room
35 Pa
Wash bay
Optional location
40 Pa
Change room
COB
30 Pa
MAL
Weigh booth 1
20 Pa
Airflow protection plenum
Return air shaft
Weigh booth 2
Broken bulk store
10 Pa
Dispensary pre-staging room
20 Pa
5 Pa
W/h staff
Warehouse area

**Fig A3.2 continued**

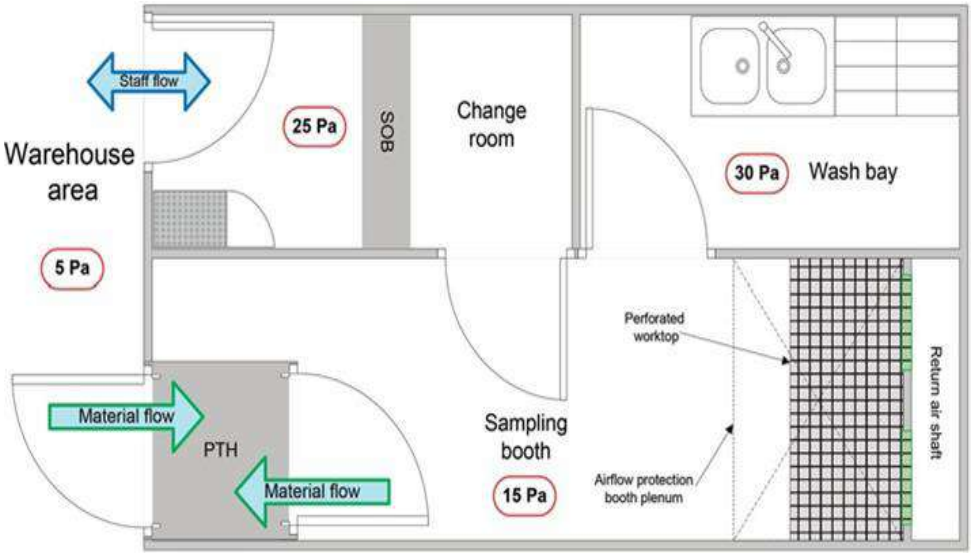



Note that the adjacent room pressures impact on determining the dispensary pressures. COB: cross-overbench; MAL:material airlock;W/h: warehouse.

Similar aspects may be considered when designing a sampling area, as materials and primary components may be exposed to the environment during sampling (for examples, see Figs A3.3 and A3.4). Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product.

**Fig. A3.3**

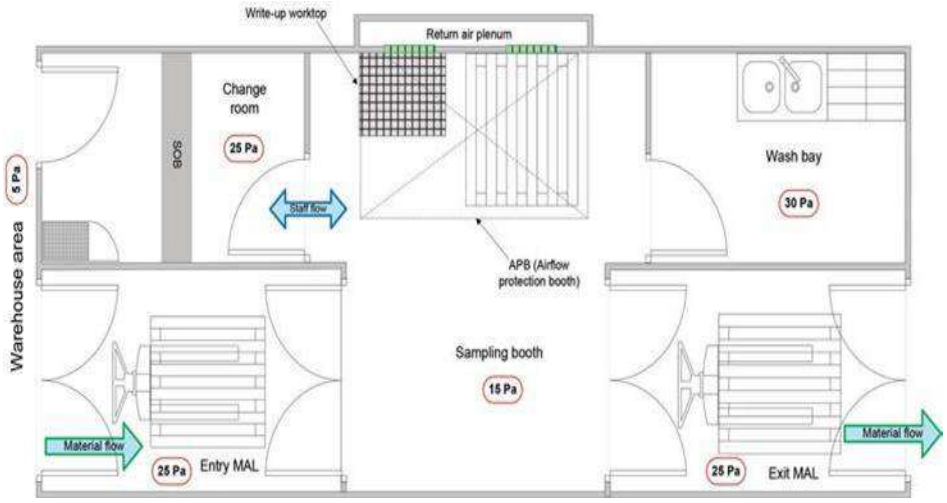
**Example of a sampling area**




PTH: pass-through hatch.

**Fig. A3.4**

**Example of a sampling area**




MAL: material airlock.

A clean corridor concept is usually recommended for non-sterile oral solid-dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms. This is to facilitate containment of dust and contaminants that may have been generated in production rooms (see the principles mentioned in the text on weighing/ dispensing and sampling areas) (for an example, see Fig. A3.5). To further support containment, consideration may also be

given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas (for an example, see Fig. A3.6). appropriately, designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place. The use of airlocks assists in ensuring containment; however, other means may be considered to achieve this objective, such as closed systems and pressure gradients between adjacent areas.

Fig. A3.5

Example of a change room and some production areas

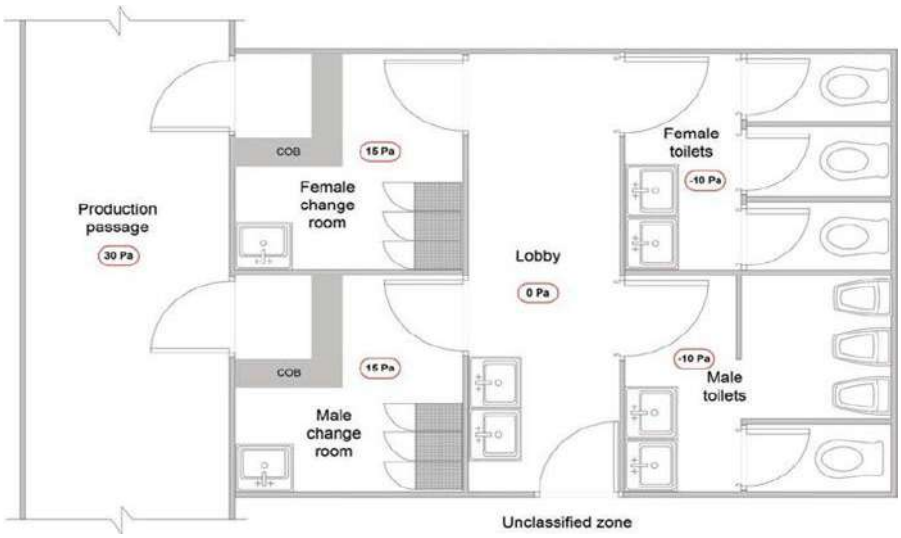
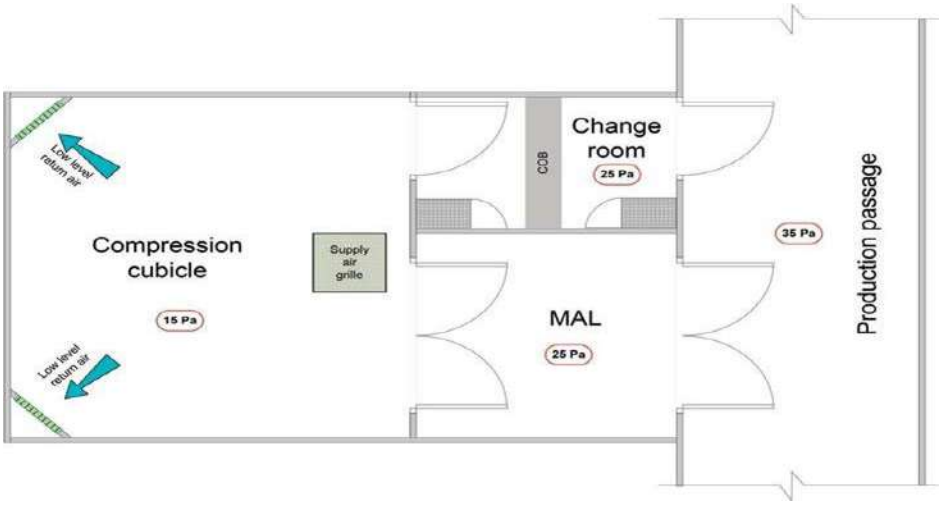



Fig. A3.6

Example of a compression cubicle with material (MAL) and personnel (PAL) airlocks (also used as an area to change garments)

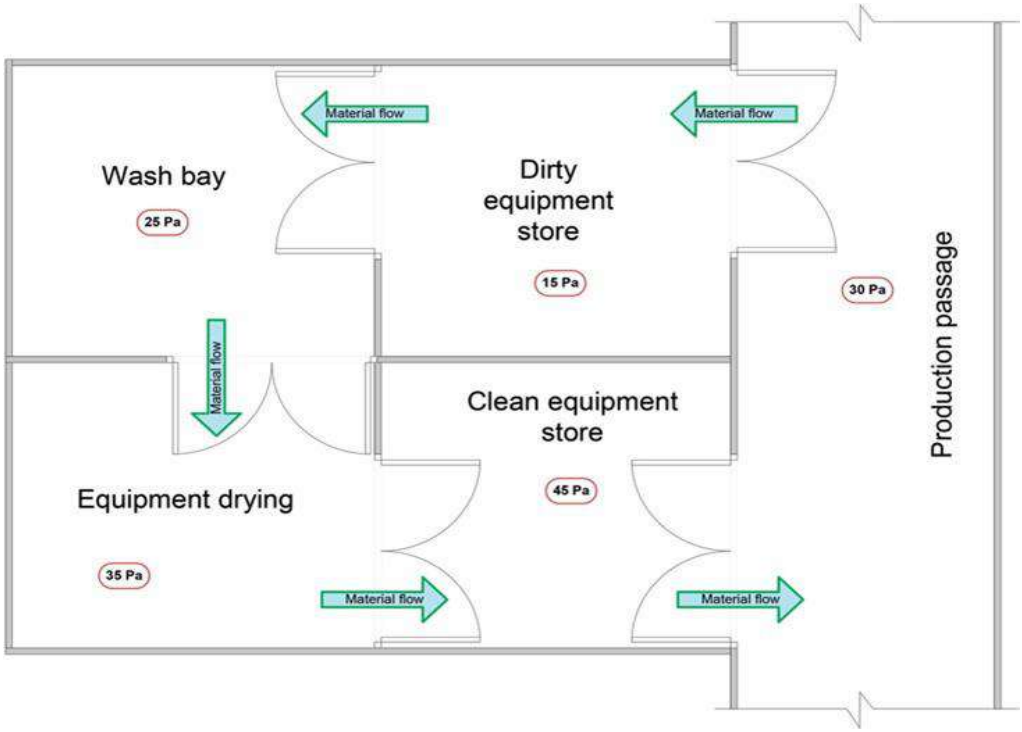



Washing areas should be designed and used in such a manner that equipment and components will not be re-contaminated after cleaning. The system supplying and extracting air from the area(s) should be suitably designed to ensure that this objective is achieved. Principles that may be considered include (but are not limited to) filtration of air, pressure differentials between areas, air

changes per hour and airflow directions (for an example, see Fig. A3.7).

**Fig. A3.7**

**Example of a washing area**




## Quality Control Area

3.28. Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biological, microbiological and radioisotopes, which should also be separated from each other.

3.29. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross contamination. There should be adequate suitable storage space for samples and records.

3.30. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.31. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

## Ancillary Area

3.32. Rest and refreshment rooms should be separate from other areas.

3.33. Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.34. Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.35. Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

## CHAPTER FOUR-EQUIPMENT

## Principle

Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

## General Requirement

4.1. Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

4.2. Repair and maintenance operations should not present any hazard to the quality of the products.

4.3. Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

4.4. Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

4.5. Equipment should be installed in such a way as to prevent any risk of error or of contamination.

4.6. Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

4.7. Balances and measuring equipment of an appropriate range and precision should be available

4.8. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

4.9. Fixed pipe work should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

4.10. Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that details the alarm and action limits for microbiological contamination and the measures to be taken.

4.11. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

## CHAPTER FIVE-MATERIALS

### Principles

The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging). Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

### General

5.1. No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

5.2. All incoming materials and finished products should be quarantined immediately after receipt or processing and inspection, until they are released for use or distribution.

5.3. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly manner to permit batch segregation and stock rotation by First Expiry First Out and/or First In First Out rule.

5.4. Appropriate stock management system and procedures should be established with the use of bin cards and stock cards or any fully validated electronic record system.

5.5. Materials should not be kept directly in contact with floors, nearer to walls and ceilings in order to allow appropriate space for cleaning and inspection.

5.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

### Starting Materials

5.7. The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

5.8. Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

5.9. For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

5.10. All incoming materials should be checked to ensure that the consignment correspondsto the order. Containers should be cleaned where necessary and labelled, if required,with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

5.11. Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

5.12. If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.13. Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference whereapplicable;
(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
(c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

5.14. There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Each incoming API containers should be sampled at least for identification unless otherwise appropriately justified (See Quality Control Chapter).
5.15. Only starting materials released by the quality control department and within theirshelf-life and/or retest period should be used for production.
5.16. Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
5.17. Each dispensed material and its weight or volume should be independently checked and recorded.
5.18. Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such (See also Production).

## Packaging Materials

5.19. The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
5.20. Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.
5.21. Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
5.22. Out-dated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.
5.23. All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

## Intermediate and Bulk Products

5.24. Intermediate and bulk products should be kept under appropriate conditions.
5.25. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

## Finished Products

5.26. Finished products should be held in quarantine until their final release, after which they

should be stored as usable stock under conditions established by the manufacturer.

5.27. The evaluation of finished products and the documentation necessary for release of a product for sale are described under "Good practices in quality control".

## Rejected, Recovered, Reprocessed and Reworked Materials

5.28. Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

5.29. The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, andif it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

5.30. The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf- life. The recovery should be recorded.

5.31. The need for additional testing of any finished product that has been reprocessed reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

## Recalled Products

5.32. Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

## Returned Products

5.33. Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabeling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

## Reagents and Culture Media

5.34. There should be records for the receipt and preparation of reagents and culture media.

5.35. Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the Storage conditions. The label should be signed and dated by the person preparing the reagent.

5.36. Both positive and negative controls should be applied to verify the suitability of culture

media each time they are prepared and used. The size of the inoculums used in positive controls should be appropriate to the sensitivity required.

## Reference Standards

5.37. Whenever official reference standards exist, these should preferably be used.

5.38. Official reference standards should be used only for the purpose described in the appropriate monograph.

5.39. Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

5.40. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

5.41. Reference standards should be properly labelled with at least the following information:
(a) name of the material;
(b) batch or lot number and control number;
(c) date of preparation;
(d) shelf-life;
(e) potency;
(f) storage conditions.

5.42. All in-house reference standards should be standardized against an official reference standard, initially and at regular intervals thereafter.

5.43. All reference standards should be stored and used in a manner that will not adversely affect their quality.

## Waste Materials

5.44. Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate and enclosed cupboards.

5.45. Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

## Miscellaneous

5.46. Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in- process materials or finished products.

## CHAPTER SIX-PERSONNEL

### Principle

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of quality products relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks, which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practicethat affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

### General

6.1. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

6.2. The manufacturer must have an organisation chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authorityto carry out their responsibilities. Their duties may be delegated to designated deputiesof a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

### Key Personnel

6.3. Key Personnel includes the head of Production, the head of Quality Control, the head of engineering and if at least one of these persons is not responsible for the release of products the authorised person(s) designated for the purpose (Quality Assurance Head). Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other.

6.4. The head of the Production Department generally has the following responsibilities:

a) ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
b) approve the instructions relating to production operations and to ensure their strict implementation;
c) ensure that the production records are evaluated and signed by an authorised person;
d) check the maintenance of his department, premises and equipment;
e) ensure that the appropriate validations are done;
f) ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

6.5. The head of the Quality Control Department generally has the following responsibilities:

a) approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
b) evaluate batch records;
c) ensure that all necessary testing is carried out;
d) approve specifications, sampling instructions, test methods and other Quality Control procedures;
e) approve and monitor any contract analysts;

f) check the maintenance of his department, premises and equipment;
g) ensure that the appropriate validations are done;
h) ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

6.6. The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

a) The authorization of written procedures and other documents, including amendments;
b) the monitoring and control of the manufacturing environment;
c) plant hygiene;
d) process validation;
e) training;
f) the approval and monitoring of suppliers of materials;
g) the approval and monitoring of contract manufacturers;
h) the designation and monitoring of storage conditions for materials and products;
i) the retention of records;
j) the monitoring of compliance with the requirements of GMP;
k) the inspection, investigation, and taking of samples, in order to monitor factorswhich may affect product quality.

6.7. The quality assurance head (authorized and/or designated person (s)) shall have the following general responsibilities:

a) Ensuring compliance with technical or regulatory requirement and other national legislation and international standards as applicable;
b) Implementation and when needed establishment of the quality system of the company.
c) Participation in the development of the company's quality manual.
d) Approval of a batch for release of products for sales.
e) Conformation that the marketing authorization and the manufacturing authorization requirements for the product have been met;
f) Conformation that installed manufacturing premises, equipment and testing procedures have been validated and/or qualified;
g) Setting QA compliance objectives and ensuring that targets are achieved;
h) Ensures that the principles and guidelines of cGMP, as laid down in these guidelines and other applicable international standards have been followed;
i) Retention of records;
j) Supervises and ensures that appropriate audits and self inspection are carried out by experienced and trained staff in a team;
k) Any planned changes or deviations in manufacturing or quality control have been notified in accordance with defined written system before any implementation and product release;
l) Review and approval of Master Manufacturing and Packaging Record;
m) Review of all QC testing results, production documents, results of in-process control and overall compliance to the specification for the finished product prior to release.
n) Review and approval of Qualification & Validation Protocols and reports;
o) Liaise with the production and quality control heads and staffs that QA system is functioning properly;
p) Identifying relevant quality–related training needs and delivering training.
q) Ensures that annual product quality review is done as planned

## Training

6.8. The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

6.9. Beside the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

6.10. Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

6.11. Visitors or untrained personnel should, preferably, not be taken into the production and Quality Control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

6.12. The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

## Personnel Hygiene

6.13. Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

6.14. All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

6.15. Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

6.16. Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

6.17. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

6.18. Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

6.19. Personnel should be instructed to use the hand-washing facilities.

6.20. Any specific requirements for the manufacture of special groups of products, for example sterile preparations, hazardous substances are covered in the Supplementary Guidelines.

## CHAPTER SEVEN-PRODUCTION

### Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

### General

7.1. Production should be performed and supervised by competent people.
7.2. All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and should be recorded.
7.3. All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.
7.4. Damage to containers and any other problem which might adversely affect the quality
7.5. Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
7.6. Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
7.7. All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
7.8. Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
7.9. Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross contamination.
7.10. At every stage of processing, products and materials should be protected from microbial and other contamination.
7.11. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.
7.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.
7.13. Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean, etc.).
7.14. Checks should be carried out to ensure that pipelines and other pieces of equipmentused for the transportation of products from one area to another are connected in a correct manner.
7.15. Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent authorized person, with the involvement of the Quality Control Department when appropriate.
7.16. Access to production premises should be restricted to authorised personnel.
7.17. Production of non-medicinal products should be avoided in areas and with the equipment

destined for the production of medicinal products.

## Prevention of Cross Contamination in Production

7.18. Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxic, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

7.19. Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a. production in segregated areas (required for products such as penicillins, cephalosporins, steroids, cytotoxic, live vaccines, live bacterial preparations and some other biological etc );
b. providing appropriate air-locks and air extraction;
c. minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
d. keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
e. using cleaning and decontamination procedures of known effectiveness, asineffective cleaning of equipment is a common source of cross-contamination;
f. using "closed systems" of production;
g. testing for residues and use of cleaning status labels on equipment.

7.20. Measures to prevent cross-contamination and their effectiveness should be checked periodically according to written standard procedures.

## Validation

7.21. Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

7.22. When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

7.23. Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

7.24. Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

## Starting Materials

7.25. The purchase and handling of starting materials during processing and/or production should

meet the requirements GMP for Materials described in this guideline.

7.26. Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used for production.

7.27. Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

7.28. Each dispensed material and its weight or volume should be independently checked and recorded.

7.29. Materials dispensed for each batch should be kept together and conspicuously labelled as such.

## Processing Operation-Intermediate and Bulk

7.30. Before any processing operation is started, step should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

7.31. Intermediate and bulk products should be kept under appropriate conditions.

7.32. Critical processes should be validated.

7.33. Any necessary in-process controls and environmental controls should be carried out and recorded.

7.34. Any significant deviation from the expected yield should be recorded and investigated with appropriate correctives measures.

## Packaging Operations

7.35. When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

7.36. Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free fromany products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

7.37. The name and batch number of the product being handled should be displayed at each packaging station or line.

7.38. All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

7.39. Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

7.40. Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

7.41. The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

7.42. Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

7.43. Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

7.44. Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

7.45. On-line control of the product during packaging should include at least checking the following:

a) general appearance of the packages;
b) whether the packages are complete;
c) whether the correct products and packaging materials are used;
d) whether any over-printing is correct;
e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

7.46. Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

7.47. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

7.48. Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

# CHAPTER EIGHT-QUALITY CONTROL

## Principle

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

## General

8.1. Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

8.2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

8.3. Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

8.4. Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

## Good Quality Control Laboratory Practice

8.5. Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

8.6. The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed under Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

## Documentation

8.7. Laboratory documentation should follow the principles given under Documentation chapter. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

a) specifications;
b) sampling procedures;
c) testing procedures and records (including analytical worksheets and/or laboratory notebooks);
d) analytical reports and/or certificates;
e) data from environmental monitoring, where required;
f) validation records of test methods, where applicable;
g) procedures for and records of the calibration of instruments and maintenance of equipment.

8.8. Any Quality Control documentation relating to a batch record should be retained forone year after the expiry date of the batch.

8.9. For some kinds of data (e.g. analytical tests results, yields, environmental controls, etc.) it is recommended that records in a manner permitting trend evaluation be kept.

8.10. In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

## Sampling

8.11. The sample taking should be done in accordance with approved written procedures that describe:
a) the method of sampling;
b) the equipment to be used (scoops, spatula, dip tubes, different sampling spears,sample thieves, etc;
c) the amount of the sample to be taken;
d) the type and condition of the sample container to be used;
e) the identification of containers sampled;
f) any special precautions to be observed, especially with regard to the sampling ofsterile or noxious materials;
g) the storage conditions;
h) instructions for the cleaning and storage of sampling equipment.

8.12. Reference samples for retention should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

8.13. Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

8.14. Reference samples retained from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit full re-examination. Reference sample for the purpose of retention does not include samples collected for stability monitoring.

## Testing

8.15. Analytical methods should be validated. All testing operations described in the marketing authorisation should be carried out according to the approved validated test methods.

8.16. The results obtained should be recorded and checked to make sure that they areconsistent with each other. Any calculations should be critically examined.

8.17. The tests performed should be recorded and the records should include at least thefollowing data:

a) Name of the material or product and, where applicable, dosage form;
b) Batch number and, where appropriate, the manufacturer and/or supplier;
c) References to the relevant specifications and testing procedures;
d) Test results, including observations and calculations, and reference to anycertificates of analysis;
e) Dates of testing;
f) Name and signature of the persons who performed the testing;
g) Name and signature of the persons who verified the testing and the calculations, where appropriate;
h) A clear statement of release or rejection (or other status decision) and the datedsignature of the designated responsible person.

8.18. All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

8.19. Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

8.20. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of reagents (where applicable) and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

8.21. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

8.22. Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

### Stability Study Monitoring

8.23. Quality control should evaluate the stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products in line with the marketing authorization of the product.

8.24. Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to intend marketing storage conditions (See also guideline for

Registration).

8.25. A written programme for stability determination should be developed and implemented to include elements such as:

a) complete description of the drug involved in the study;
b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
c) provision for the inclusion of a sufficient number in line with the registrationguideline;
d) the testing schedule for each drug ;
e) provision for special storage conditions;
f) provision for adequate sample retention;
g) a summary of all the data generated, including the evaluation and the conclusions of the study.

8.26. Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

8.27. After marketing, the stability of the product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities, or dissolution profile) associated with the formulation in the marketed package.

8.28. The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

8.29. This mainly applies to the products in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period (more than 30 days) before being packaged and/or shipped from a manufacturing site to a packaging site, the impact onthe stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods (more than 30 days). Stability studies on reconstituted product are performed during product development as part of compatibility study with diluents.

8.30. The on-going stability programme should be described in a written protocol following the general rules of documentation and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Qualification and Validation.

8.31. Normally, the protocol for the on-going stability programme should be the same as that of the initial long-term stability study as submitted in the marketing authorisation dossier however different protocols for on-going stability study can be considered acceptable provided that this is justified and documented in the protocol.

8.32. The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing

may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

8.33. In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

8.34. Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review during inspection and/or upon request for the purpose of marketing authorization.

8.35. Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the Authority immediately. The possible impact on batches on the market should be considered and the manufacturer should immediately consult the Authority whenever such scenarios are encountered.

8.36. A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

## CHAPTER NINE-CONTRACT PRODUCTION AND ANALYSIS

### Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings, which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor, which clearly establishes the duties of each party. The contract must clearly state the way in which the authorised person releasing each batch of product for sale exercises his full responsibility.

### General

9.1. There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

9.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorisation for the product concerned.

### The contract giver

9.3. The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in this Guide are followed.

9.4. The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

9.5. The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by an authorised person.

#### The contract acceptor

9.6. The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorisation.

9.7. The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

9.8. The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

9.9. The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analysed for the Contract Giver.

## The contract

9.10. A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and controlof the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorisation and agreed by both parties.

9.11. The contract should specify the way in which the authorised person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorisation.

9.12. The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in- process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

9.13. Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedure of the contract giver.

9.14. The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

9.15. In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Authority.

## CHAPTER TEN-COMPLAINTS AND PRODUCT RECALL

### Principle

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies,a system should be designed to recall, if necessary, promptly and effectively for products known or suspected to be defective from the market.

### Complaints

10.1. There should be designated person responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him.

10.2. There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

10.3. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

10.4. If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected.In particular, other batches which may contain reworks of the defective batch should be investigated.

10.5. All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

10.6. Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

10.7. Special attention should be given to establishing whether a complaint was causedbecause of counterfeiting.

10.8. The Authority should be informed if a manufacturer is considering recall and other action following possibly faulty manufacture, product deterioration and detection of counterfeiting or any other serious quality problems with a product.

### Recall

10.9. There should be designated person responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation.

10.10. There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

10.11. Recall operations should be capable of being initiated promptly and at any time within 24hr.

10.12. The Authority should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.

10.13. The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical

samples distributed for health professional as part of promotional activity.

10.14. Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

10.15. The progress of the recall process should be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

10.16. The effectiveness of the arrangements for recalls should be evaluated regularly.

## CHAPTER ELEVEN- SELF INSPECTION AND QUALITY AUDITS

### Principle

Self-inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures. All recommendations for corrective action should be implemented. The procedure for self- inspection should be documented, and there should be an effective follow-up programme.

### General

11.1. Personnel matters, storage of starting materials and finished products ,premises, equipment, calibration status of instrument, documentation, production and in-process controls, quality control, sanitation and hygiene, validation program, distribution of the medicinal products, arrangements for dealing with complaints and recalls and results of previous self-inspection should be examined and audited at intervals (at least once in a year) following a pre-arranged self-inspection programme in order to verify their conformity with the principles of Quality Assurance and GMP.

11.2. Self-inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

11.3. All self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded. In another words, the inspection report should include self inspection result, evaluation and conclusion and recommended corrective action

11.4. It may be useful to supplement self inspection with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audit may also extend to suppliers and contractors.

11.5. The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

11.6. Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required,it should determine the supplier's ability to conform to GMP standards

## CHAPTER TWELVE- VALIDATION AND QUALIFCATION

### Principles

It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

### Validation

12.1. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

12.2. The VMP should be a summary document which is brief, concise and clear.

12.3. The VMP should contain data on at least the following:

a) Validation policy;
b) Organisational structure of validation activities;
c) Summary of facilities, systems, equipment and processes to be validated;
d) Documentation format: the format to be used for protocols and reports;
e) Planning and scheduling;
f) Change control;
g) Reference to existing documents.

12.4. In case of large projects, it may be necessary to create separate validation master plans.

12.5. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

12.6. A report that cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification. .

12.7. The departments responsible for the qualification and validation work should approve the completed report

12.8. The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful.

12.9. The quality assurance department should approve the report after the final review .the criteria for approval should be in accordance with the companies quality assurance system

### Qualification

### Design Qualification

12.10. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).

12.11. The compliance of the design with GMP should be demonstrated and documented.

### Installation Qualification

12.12. Installation qualification (IQ) should be performed on new or modified facilities,systems and equipment.

12.13. IQ should include, but not be limited to the following:

a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
b) collection and collation of supplier operating and working instructions and maintenance requirements;
c) calibration requirements;
d) verification of materials of construction.

### Operational Qualification

12.14. Operational qualification (OQ) should follow Installation qualification.

12.15. OQ should include, but not be limited to the following:

a) tests that have been developed from knowledge of processes, systems and equipment;
b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, including “worst case” conditions.

12.16. The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

### Performance Qualification

12.17. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

12.18. PQ should include, but not be limited to the following:

a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
b) Tests to include a condition or set of conditions encompassing upper and lower operating limits.

12.19. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

## Process Validation

## General

12.20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and revalidation.

12.21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).

12.22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.

12.23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

## Prospective Validation

12.24. Prospective validation should include, but not be limited to the following:

(a) short description of the process;
(b) summary of the critical processing steps to be investigated;
(c) list of the equipment/facilities to be used (including measuring /monitoring / recording equipment) together with its calibration status
(d) finished product specifications for release;
(e) list of analytical methods, as appropriate;
(f) proposed in-process controls with acceptance criteria;
(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
(h) sampling plan; that considers –where ,when, how, how many and howmuch(sample size)
(i) methods for recording and evaluating results
(j) functions and responsibilities;
(k) proposed timetable.

12.25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters would constitute a validation of the process.

12.26. Batches made for process validation should be the same size as the intended industrial scale batches.

12.27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorisation.

## Concurrent Validation

12.28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.

12.29. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

12.30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

12.31. The results of process validation should be documented in the validation report. As a minimum, the report should include:

- A description of the process: batch/packaging document, including details of critical steps;

- A detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included, reference should be made to the sources used and where it can be found;
- any work done in addition to that specified in the protocol, or any deviations from the protocol should be formally noted along with an explanation;
- A review and comparison of the results with those expected; and
- Formal acceptance or rejection of the work by the team or persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

## Retrospective Validation

12.32. Retrospective validation is only acceptable for well-established processes (i.e. marketing of the product for not less than 5year, not less than 10 batches per year and/or NLT 25 batches over the past three years) and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment and sterile products.

12.33. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

12.34. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

12.35. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

12.36. For retrospective validation, generally data from ten to 25 consecutive batches should be examined to assess process consistency, but fewer batches not less than 10 may be examined if justified.

## Qualification of Established (in use) Facilities, Systems and Equipment

12.37. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment that have been “in use” fora period of time, and which had not been subjected to installation and or operational qualification. These should include calibration, cleaning, and preventative maintenance, operating procedures, operator training procedures and records.

## Cleaning Validation

12.38. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

12.39. Validated analytical methods having sensitivity to detect residues or contaminants should

be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

12.40. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.

12.41. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a "worst case" approach can be carried out which takes account of the critical issues.

12.42. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

12.43. "Test until clean" is not considered an appropriate alternative to cleaning validation.

12.44. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

### Change Control

12.45. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

12.46. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

## Computerized System

## Principle

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality control should not alter the need to observe the relevant principlesgiven elsewhere in the this Guideline. Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

### General

12.47. It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerised system.

12.48. The use of a computer system includes different stages. These are planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.

12.49. The purpose of validation of a computer system is to ensure an acceptable degree of evidence (documented, raw data), confidence (dependability and thorough, rigorous achievement of predetermined specifications), intended use, accuracy, consistency and reliability.

12.50. Both the system specifications and functional specifications should be validated.

12.51. Periodic (or continuous) evaluation should be performed after the initial validation.

12.52. There should be written procedures for performance monitoring, change control, programme and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation.

12.53. Aspects of computerized operations that should be considered during validation include:

a. networks
b. manual back-ups
c. input/output checks
d. process documentation
e. monitoring
f. alarms
g. shut down recovery.

## System

12.54. Attention should be paid to installation of equipment in suitable conditions where extraneous factors cannot interfere with the system. The following aspects should be considered during installation of computer system: location, power supply, temperature, and magnetic disturbances. Fluctuations in the electrical supply can influence computer systems and power supply failure can result in loss of memory and data.

12.55. A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in whichthe computer is used and how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating programme and test programme.

12.56. The software is a critical component of a computerised system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.

12.57. The system should include, where appropriate, built-in checks of the correct entry and processing of data.

12.58. Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.

12.59. Data should only be entered or amended by persons authorised to do so. Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards,

personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation, and alteration of authorisation to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.

12.60. When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by

validated electronic means.

12.61. The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorised and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments.

12.62. Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change. Such an alteration should only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.

12.63. For quality auditing purposes, it should be possible to obtain meaningful printed copies of electronically stored data.

12.64. Data should be secured by physical or electronic means against wilful or accidental damage. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.

12.65. Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.

12.66. There should be available adequate alternative arrangements for systems which needto be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.

12.67. The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.

12.68. A procedure should be established to record and analyse errors and to enable corrective action to be taken.

12.69. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency.

12.70. When the release of batches for sale or supply is carried out using a computerised system, the system should recognise that only an Authorised Person can release the batches and it should clearly identify and record the person releasing the batches.

## Validation

12.71. The extent of validation necessary will depend on a number of factors including the use to which the system is to be applied, whether it is prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of

planning, specification, programming, testing, commissioning, documentation,operation, monitoring and changing.

12.72. The computer-related systems and vendors should be defined and the vendor and product should be evaluated. The system should be designed and constructed, taking into consideration the types, testing and quality assurance of the software.

12.73. After installation of the system it should be qualified. The extent of the qualification should depend on the complexity of the system. The system should be evaluated and performance qualification, change control, maintenance and calibration, security, contingency planning, SOPs, training, performance monitoring and periodic re-evaluation should be addressed.

## Hardware Validation

12.74. As part of the validation process appropriate tests and challenges to the hardware should be performed.

12.75. Static, dust, power-feed voltage fluctuations and electromagnetic interference could influence the system. The extent of hard ware validation should depend on the complexity of the system. Hardware is considered to be equipment, and the focus should be on location, maintenance and calibration of hardware, as well as on validation/qualification.

12.76. The validation/qualification of the hardware should prove:

a. that the capacity of the hardware matches its assigned function (e.g. different language);
b. that it operates within the operational limits (e.g. memory, connector ports, input ports);
c. that it performs acceptably under worst-case conditions (e.g. long hours,temperature extremes); and
d. reproducibility/consistency (e.g. by performing at least three runs under different conditions).

12.77. The computer hard ware validation should be done in accordance with written qualification protocols and the results should be recorded in the qualification report. Revalidation should be performed when significant changes are made. Much of the hardware validation may be performed by the computer vendor. However, the ultimate responsibility for the suitability of equipment used remains with the manufacturer.

12.78. Hardware validation data and protocols should be kept by the company. When validation information is produced by an outside firm, e.g. computer vendor, the records maintained by the company need not include all of the voluminous test data; however, such records should be sufficiently complete (including general results and protocols) to allow the company to assess the adequacy of the validation. A mere certification of suitability from the vendor, for example, will be inadequate.

## Software Validation

12.79. Software is the term used to describe the complete set of programmes used by a computer, and which should be listed in a menu. Records are considered as software; focus is placed on accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction.

12.80. The company should identify the following key computer programmes: language, name, function (purpose of the programme), input (determine inputs), output

(determine outputs), fixed set point (process variable that cannot be changed by the operator), variable set point (entered by the operator), edits (reject input/output that does not conform to limits and minimize errors, e.g. four- or five-character number entry), input manipulation (and equations) and programme overrides (e.g. to stop a mixer before time).

12.81. Software validation should provide assurance that computer programmes (especially those that control manufacturing and processing) will consistently perform as they are supposed to, within pre-established limits.

12.82. When planning the validation of computer software system, the following points should be considered.

a. Function: does the programme match the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)?

b. Worst case: perform validation under different conditions (e.g. speed, data volume, frequency).
c. Repeats: sufficient number of times (replicate data entries).
d. Documentation: protocols and reports.
e. Revalidation: needed when significant changes are made.

## Analytical Method Validation

## Principle

Manufacturers should choose analytical validation protocol and procedures most suitable for testing of the product. The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose. Analytical methods, whether or not they indicate stability, should be validated. The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

## General

12.83. There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.
12.84. Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non- pharmacopoeial methods") as approved in the marketing authorization by the authority may be used.
12.85. Well-characterized reference materials, with documented purity, should be used in the validation study.
12.86. The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing, determination of particle size and residual solvents.
12.87. The results of analytical procedures should be reliable, accurate and reproducible.
12.88. Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.
12.89. The verification or degree of revalidation depends on the nature of the change(s). There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency").

## Pharmacopoeial method

12.90. When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (method verification).
12.91. Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).

## Non-pharmacopoeial method

12.92. Non-pharmacopoeial methods should be appropriately fully validated.

## Method Validation

12.93. Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.

12.94. Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.

12.95. Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.

## Characteristics of analytical validation

12.96. The analytical characteristics that should be considered during validation of analytical methods are; specificity, linearity, range, accuracy, precision, detection limit, quantitation limit, robustness.

a) *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. *Note:* it is acceptable to use a "spiked" placebo wherea known quantity or concentration of a reference material is used.

b) *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

c) *Repeatability* should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

d) *Intermediate precision* expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

e) *Reproducibility* expresses *precision* between laboratories.

f) *Robustness* (or *ruggedness*) is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters. Factors that can have an effect on robustness when performing chromatographic analysis include:

i. stability of test and standard samples and solutions;
ii. reagents (e.g. different suppliers);
iii. different columns (e.g. different lots and/or suppliers);
iv. extraction time;
v. variations of pH of a mobile phase;
vi. variations in mobile phase composition;
vii. temperature; and
viii. flow rate

g) *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used.

h) *Range* is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

i) *Specificity* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

j) *Detection limit* (*limit of detection*) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

i. visual evaluation;
ii. signal to noise ratio;
iii. standard deviation of the response and the slope;
iv. standard deviation of the blank; and
v. calibration curve

k) *Quantitation limit* (*limit of quantitation*) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

i. visual evaluation;
ii. signal to noise ratio;
iii. standard deviation of the response and the slope;
iv. standard deviation of the blank; and
v. calibration curve.

## System Suitability Testing

12.97. System suitability testing is an integral part of many analytical procedures and method validation. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established fora particular procedure depend on the type of procedure being evaluated, for instance,a resolution test for an HPLC procedure.

## Revalidation

12.98. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

# CHAPTER THIRTEEN-DOCUMENTATION

## Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

## General

13.1. Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

13.2. Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

13.3. Procedures give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, and equipment operations.

13.4. Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.

13.5. Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorisation dossiers.

13.6. Documents should be approved, signed and dated by appropriate and authorised persons.

13.7. Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced throughthe reproduction process.

13.8. Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

13.9. Documents should not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

13.10. Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

13.11. The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

13.12. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result

of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughoutthe period of retention.

## Essential Documents Specifications

13.13. There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

## Specifications for starting and packaging materials

13.14. Specifications for starting and primary or printed packaging materials should include:

a. description of the materials, including: the designated name and the internal code reference;
   i. the reference, if any, to a pharmacopoeial monograph;
   ii. the approved suppliers and, if possible, the original producer of the products;
   iii. a specimen of printed materials;
b. directions for sampling and testing or reference to procedures;
c. qualitative and quantitative requirements with acceptance limits;
d. storage conditions and precautions;
e. the maximum period of storage before re-examination.

## Specifications for intermediate and bulk products

13.15. Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

## Specifications for Finished Products

13.16. Specifications for finished products should include:

a) the designated name of the product, reference number, version, date ofauthorization, date of revision;
b) the formula or a reference to the manufacturing and/or master formula;
c) description of the pharmaceutical form and package details;
d) directions for sampling and testing or a reference to procedures;
e) the qualitative and quantitative requirements, with the acceptance limits;
f) the storage conditions and any special handling precautions, where applicable;
g) the shelf-life.

## Batch Formula and Processing Instruction

13.17. Formally authorised Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document and named master formula.

*The Manufacturing Formula should include:*

a) the name of the product, with a product reference code relating to its specification;
b) a description of the pharmaceutical form, strength of the product and batch size;
c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material;
d) mention should be made of any substance that may disappear in the course of processing;
e) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

*The Processing Instructions should include*:

a) a statement of the processing location and the principal (key) equipment to be used;
b) the methods, or reference to the methods, to be used for preparing the criticalequipment (e.g. cleaning, assembling, calibrating, sterilising);
c) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
d) the instructions for any in-process controls with their limits;
e) where applicable, the requirements for bulk storage of the products; including the container, labelling and special storage conditions;
f) any special precautions to be observed where applicable.

## Packaging Instructions

13.18. There should be formally authorised Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:

a) name of the product;
b) description of its pharmaceutical form, and strength where applicable;
c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;
f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
h) details of in-process controls with instructions for sampling and acceptance limits.

## Batch Processing Records

13.19. A Batch Processing Record should be kept for each product batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions (Master Formula). The method of preparation of such records should be designed to avoid transcription errors. The record should carry the numberof the batch being manufactured.

13.20. Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

13.21. During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

a) the name of the product;
b) dates and times of commencement, of significant intermediate stages and of completion of production;
c) name of the person responsible for each stage of production;
d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
f) any relevant processing operation or event and major equipment used;
g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
h) the amount of product yield obtained at different and pertinent stages of manufacture;
i) notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

## Batch Packaging Records

13.22. A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed,as well as the batch number and the planned quantity of finished product that will be obtained.

13.23. Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

13.24. The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

a) the name of the product;
b) the date(s) and times of the packaging operations;
c) the name of the responsible person carrying out the packaging operation;
d) the initials of the operators of the different significant steps;
e) records of checks for identity and conformity with the Packaging Instructions including the results of in-process controls;

f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
g) whenever possible, samples of printed packaging materials used, includingspecimens of the batch coding, expiry dating and any additional overprinting;
h) notes on any special problems or unusual events including details with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

## Procedures and Records

### *Receipt*

13.25. There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material. The records of the receipts should include:

a) the name of the material on the delivery note and the containers;
b) the "in-house" name and/or code of material (if different from a);
c) date of receipt;
d) supplier's name and, if possible, manufacturer's name;
e) manufacturer's batch or reference number;
f) total quantity, and number of containers received;
g) the batch number assigned after receipt;
h) any relevant comment (e.g. state of the containers).

13.26. There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

### *Sampling*

13.27. There should be written procedures for sampling, which include the person(s) authorised to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

### *Testing*

13.28. There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

### *Other*

13.29. Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the authorised person(s) designated for the purpose.

13.30. Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

13.31. There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:

a. validation;
b. equipment assembly and calibration;

c. maintenance, cleaning and sanitization;
d. personnel matters including training, clothing, hygiene;
e. environmental monitoring;
f. pest control;
g. complaints;
h. recalls;
i. returns.

13.32. Clear operating procedures should be available for major items of manufacturing and test equipment.

13.33. Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

13.34. Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

# CHAPTER FOURTEEN-WATER FOR PHARMACEUTICAL USE

## Principle

Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. These include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health.

Different grades of water quality are required depending on the route of administration of the pharmaceutical products. Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a systemon demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use. It is very important to minimize microbial contamination by routine sanitization and taking appropriate measures to prevent microbial proliferation.

## General

14.1. Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

14.2. The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for planned preventive maintenance tasks, they need not be approved after implementation.

14.3. Water sources and treated water should be monitored regularly for quality and for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water purification, storage and distribution systems should also be monitored. Records of the monitoring results and any actions taken should be maintained for an appropriate length of time.

14.4. Where chemical sanitization of the water systems is part of the bio-contamination control programme, a validated procedure should be followed to ensure that the sanitizing agent has been effectively removed.

## Water Quality Specification

14.5. Pharmacopoeial requirements for WPU are described in the international and other pharmacopoeias and limits for various contaminants are given. Manufacturers should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

## Drinking Water

14.6. Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.

14.7. Drinking-water is unmodified except for limited treatment of the water derived from a natural or stored source. Typical treatment includes softening, removal of specific ions, particle reduction and antimicrobial treatment. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water will dictate the treatment required to render it safe for human consumption (drinking). It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It is also commonfor public water supply organizations to conduct tests and guarantee that the drinking water delivered is of potable quality. Such test certificates can be used by the manufacturer as a basis for establishment of quality specification of drinking water. Drinking water should meet the requirements of WHO and ISO drinking water guideline.

14.8. If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site to confirm that the quality meets the standards required for potable water.

## Purified Water

14.9. Purified water (PW) should be prepared from a potable water source as a minimum- quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

## Water for Injection

14.10. Water for injections (WFI) should be prepared by distillation as a final purification step from potable water as a minimum-quality feed-water. WFI is not sterile water and is not a final dosage form. It is an intermediate bulk product. WFI is the highest quality of pharmacopoeial WPU.

14.11. Besides distillation, there are alternative ways to produce water for injection as long as the WFI complies with the specifications stated in the most recent monographs of the relevant pharmacopoeias approved by the EFDA. Stages include, but are not limited to, the collection and treatment of source water; treatment of drinking water; treatment of purified water; and the production, storage, distribution, use and control of WFI.

14.12. Principles of risk management (3) and data governance should be applied in each relevant stage of the life-**c**ycle.

## Other Grades of Water

14.13. When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

### Application of Specific Water for Dosage Form Processing

14.14. The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

14.15. Highly Purified Water can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for WFI.

14.16. Water for Injection should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for sterile water for preparation of injections. WFI should alsobe use d for the final rinse after cleaning of equipment and components that come into contact with injectable products as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

14.17. When steam comes into contact with an injectable product in its final container, or equipment for preparing injectable products, it should conform with the specification for WFI when condensed.

## Water Purification

### General

14.18. The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI.

14.19. The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method:

a. the water quality specification;
b. the yield or efficiency of the purification system;
c. feed-water quality and the variation over time (seasonal changes);
d. the reliability and robustness of the water-treatment equipment in operation;
e. the availability of water-treatment equipment on the market;
f. the ability to adequately support and maintain the water purification equipment;
g. the operation costs.

14.20. The specifications for water purification equipment, storage and distribution systems should take into account the following:

a. the risk of contamination from leachates from contact materials;
b. the adverse impact of adsorptive contact materials;
c. hygienic or sanitary design;
d. corrosion resistance;
e. freedom from leakage;
f. configuration to avoid proliferation of microbiological organisms;
g. tolerance to cleaning and sanitizing agents (thermal and chemical);
h. the system capacity and output requirements; and
i. the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.

14.21. The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

a. the space available for the installation;
b. structural loadings on buildings;
c. the provision of adequate access for maintenance; and
d. the ability to safely handle regeneration and sanitization chemicals.

## Production of Drinking Water

14.22. Drinking water is derived from a raw water source such as a well, river or reservoir. Typical processes employed at a user plant to produce potable water include:

a. filtration;
b. softening;
c. disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
d. iron (ferrous) removal;
e. precipitation; and
f. reduction of specific inorganic/organic materials.

14.23. The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking-water quality changes significantly, the direct use of this water as a WPU, or as the feed-water to downstream treatment stages, should be reviewed and the result of the review documented.

14.24. Where drinking-water is derived from an "in-house" system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or its operation should not be made until a review has been completed and the change approved by the QA department.

14.25. Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, its use should ensure a turnover of the stored water sufficient to prevent stagnation.

14.26. Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

14.27. Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained, or flushed, and sanitized.

14.28. Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back-flushing, chemical or thermal sanitization and frequent regeneration should be considered. Additionally, all water- treatment components should be maintained with continuous water flow to inhibit microbial growth.

## Production of Purified water

14.29. There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be

used to prepare PW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. Distillation can also be used.

14.30. The following should be considered when configuring a water purification system:

a. the feed-water quality and its variation over seasons;
b. the required water-quality specification;
c. the sequence of purification stages required;
d. the energy consumption;
e. the extent of pretreatment required to protect the final purification steps;
f. performance optimization, including yield and efficiency of unit treatment-process steps;
g. appropriately located sampling points designed in such a way as to avoid potential contamination; and
h. unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

14.31. Ambient-temperature PW systems are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbiological control and sanitization. The following techniques should be considered:

a. maintenance of flow through water-purification equipment at all times;
b. control of temperature in the system by pipeline heat exchange or plant-roomcooling to reduce the risk of microbial growth (guidance value <25 °C);
c. provision of ultraviolet disinfection;
d. selection of water-treatment components that can be thermally sanitized; and/or
e. application of chemical sanitization (including agents such as ozone).

## Production of Bulk water for injection

14.32. Bulk water for injections (BWFI) should be prepared from drinking water (usually with further treatment) or purified water as a minimum-quality feed water. BWFI is not sterile water and is not a final dosage form. It is an intermediate bulk product and suitable to be used as an ingredient during formulation. BWFI is the highest quality of pharmacopoeial WPU.

14.33. Certain pharmacopoeias place constraints upon the permitted purification techniques as part of the specification of the BWFI. The International Pharmacopoeia and the European Pharmacopoeia, for example, allow only distillation as the final purification step. However, WHO technical report series no 1025, 2020; annex 3 production of water for injection by means other than distillation are used with appropraite control strategy:

- the appropraiteness of user requirement specifications
- feed water quality
- the sequence of purificationns stages required
- the extent of pretreatment required
- approprely designed ad located sampling points
- control are inplace to prevent dead legs and
- In-line monitoring

14.34. BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxin) with appropriate action and alert limits.

14.35. BWFI should also be protected from recontamination and microbial proliferation.

## Water Storage and Distribution

### General

14.36. The water storage and distribution should work in conjunction with the purification plant to ensure consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment.

14.37. The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.

14.38. Once water has been purified using an appropriate method, it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following should be considered during storage and distribution systems of WPU:

a. The storage and distribution system should be configured to prevent recontamination of the water after treatment and be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.

b. The materials that come into contact with WPU, including pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives:

i. *Compatibility*. All materials used should be compatible with the temperature and chemicals used by or in the system.

ii. *Prevention of leaching*. All materials that come into contact with WPU should be non-leaching at the range of working temperatures.

iii. *Corrosion resistance*. PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipework used. Appropriate sanitary specification plastics and stainless steel materials are acceptable for WPU systems. When stainless steel is used it should be at least grade 316L. The system should be passivated after initial installation or after modification. When accelerated passivation is undertaken, the system should be thoroughly cleaned first, and the passivation process should be undertaken in accordance with a clearly defined documented procedure.

iv. *Smooth internal finish*. Once water has been purified it is susceptible to microbiological contamination, and the system is subject to the formation of biofilms when cold storage and distribution is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal finish should have an arithmetical average surface roughness of not greater than 0.8 micrometer arithmetical mean roughness (Ra). When stainless steel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless steel material to surface corrosion.

v. *Jointing*. The selected system materials should be able to be easily jointed

by welding in a controlled manner. The control of the process should include as a minimum, qualification of the operator, documentation of the welder set-up, work-session test pieces, logs of all welds and visual inspection of a defined proportions of welds.

vi. *Design of flanges or unions*. Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carriedout to ensure that the correct seals are used and that they are fitted and tightened correctly.

vii. *Documentation.* All system components should be fully documented and be supported by original or certified copies of material certificates.

viii. *Materials.* Suitable materials that may be considered for sanitary elementsof the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

## Sanitization of Water System

## Storage Vessel

14.39. The water storage vessel used in a system serves a number of important purposes. The design and size of the vessel should take into consideration the following:

a) *Capacity:* The capacity of the storage vessel should be determined on the basis of the following requirements:

i. It is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points.

ii. The water treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and equipment stress that occur when the equipment cycles on and off too frequently.

iii. The capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session or other logical period of demand.

b) *Contamination Control Consideration*: The following should be taken into account for the efficient control of contamination:

i. The headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage theproliferation of microbiological organisms. The water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.

ii. Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured.

iii. Vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally

be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered to prevent condensation within the filter matrix that might lead to filter blockage and to microbial grow through that could contaminate the storage vessels.

iv. Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.

## Water Distribution Pipe

14.40. The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled. Filtration should not usually be used in distribution loops or at take-off user points to control bio-contamination. Such filters are likely to conceal system contamination.

## Temperature Control and Heat Exchangers

14.41. Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or double plate and frame configuration should be considered. Where these types are not used, an alternative approach whereby the utility is maintained and monitored at a lower pressure than the WPU may be considered.

14.42. Where heat exchangers are used they should be arranged in continually circulating loops or sub-loops of the system to avoid unacceptable static water in systems. When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

## Circulation Pumps

14.43. Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

## Bio-contamination Control System

14.44. The following control techniques may be used alone or more commonly in combination:

a. Maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms. The maintenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short-term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur.

b. The system design should ensure the shortest possible length of pipework.

c. For ambient temperature systems, pipework should be isolated from adjacent hot pipes.
d. Deadlegs in the pipework installation greater than 1.5 times the branch diameter should be avoided.
e. Pressure gauges should be separated from the system by membranes.
f. Hygienic pattern diaphragm valves should be used.
g. Pipework should be laid to falls to allow drainage.
h. The growth of microorganisms can be inhibited by:

    i. ultraviolet radiation sources in pipework;
    ii. maintaining the system heated (guidance temperature 70–80 °C);
    iii. sanitizing the system periodically using hot water (guidance temperature >70 °C);
    iv. sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
    v. routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.

## Operational Consideration

14.45. Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

14.46. WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

14.47. WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance. The review should consider matters such as: changes made since the last review, system performance, reliability, quality trends, failure events, investigations, out-of-specifications results from monitoring, changes to the installation, updated installation documentation, log books and the status of the current SOP list.

# CHAPTER FIFTEEN-HEATING, VENTILATION AND AIR CONDITIONING SYSTERM (HVAC)

## Principle

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. A well-designed HVAC system will also provide comfortable conditions for operators. HVAC system design influences architectural layouts with regard to items such as airlock positions, doorways and lobbies. The architectural components have an effect on room pressure differential cascades and cross- contamination control. The prevention of contamination and cross-contamination is an essential design consideration of the HVAC system. In view of these critical aspects, the design of the HVAC system should be considered at the concept design stage of a pharmaceutical manufacturing plant.

## Scope

These guidelines focus primarily on the design and good manufacturing practices (GMP) requirements for HVAC systems for facilities for the manufacture of solid dosage forms. Most of the system design principles for facilities manufacturing solid dosage forms also apply to other facilities such as those manufacturing liquids, creams and ointments. These guidelines do not cover requirements for manufacturing sites for the production of sterile pharmaceutical products. These guidelines do not cover the specific requirements relating to facilities handling hazardous products.

They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation

## Protection

## Product and Personnel

15.1. Areas for the manufacture of pharmaceuticals, where pharmaceutical starting materials and products, utensils and equipment are exposed to the environment, should be classified as “clean areas”.

15.2. The achievement of a particular clean area classification depends on a number of criteria that should be addressed at the design and qualification stages. A suitable balance between the different criteria will be required in order to create an efficient clean area. Some of the basic areas to be considered are; building finishes and structure , air filtration, air change rate or flushing rate, room pressure, location of air terminals and directional airflow, temperature, humidity, material flow, personnel flow, equipment movement, process being carried out, outside air conditions, occupancy and type of product.

15.3. Air filtration and air change rates should ensure that the defined clean area classification is attained. The air change rates should be determined by the manufacturer and designer, taking into account the various critical parameters. Primarily the air change rate should be set to a level that will achieve the required

clean area classification. Air change rates normally vary between 6 and 20 air changes per hour and are normally determined by the following considerations:

a. level of protection required
b. the quality and filtration of the supply air
c. particulates generated by the manufacturing process
d. particulates generated by the operators
e. configuration of the room and air supply and extract locations
f. sufficient air to achieve containment effect
g. sufficient air to cope with the room heat load
h. sufficient air to maintain the required room pressure

15.4. In classifying the environment, the manufacturer should state whether this is achieved under 'as-built', 'at-rest' or 'operational' condition:

a. Room classification tests in the "as-built" condition should be carried out on the bare room, in the absence of any equipment or personnel.
b. Room classification tests in the "at-rest" condition should be carried out with the equipment operating where relevant, but without any operators. Because of the amounts of dust usually generated in a solid dosage facility most clean area classifications are rated for the "at-rest" condition.
c. Room classification tests in the "operational" condition should be carried out during the normal production process with equipment operating, and the normal number of personnel present in the room. Generally, a room that is tested for an "operational" condition should be able to be cleaned up to the "at-rest" clean area classification after a short clean-up time. The clean-up time should be determined through validation and is generally of the order of 20 minutes.

15.5. Materials and products should be protected from contamination and cross- contamination during all stages of manufacture. Airborne contaminants should be controlled through effective ventilation. External contaminants should be removed by effective filtration of the supply air. Internal contaminants should be controlled by dilution and flushing of contaminants in the room, or by displacement airflow.

15.6. Airborne particulates and the degree of filtration should be considered critical parameters with reference to the level of product protection required. The level of protection and air cleanliness for different areas should be determined according tothe product being manufactured, the process being used and the product's susceptibility to degradation. Examples of level of protection are indicated in the following table:

| **Level** | **Condition** | **Example of area** |
|---|---|---|
| Level 1 | General | Area with normal housekeeping and maintenance, e.g. warehousing, secondary packing |
| Level 2 | Protected | Area in which steps are taken to protect the exposed pharmaceutical starting material or product from contamination or degradation, e.g. manufacturing, primary packing, dispensing |
| Level 3 | Controlled | Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material or product |

15.7. The degree to which air is filtered plays an important role in the prevention of contamination and the control of cross-contamination. The type of filters required for different applications depends on the quality of the ambient air and the return air (where applicable) and also on the air change rates. The following table gives the recommended filtration levels for different levels of protection in a pharmaceutical facility. Manufacturers should determine and prove the appropriate use of filters:

| **Level of Protection** | **Recommended Filters** |
|---|---|
| Level 1 | Primary filters only (e.g. EN779 G4 filters) |
| Level 2 and 3 | Production facility operating on 100% outside air: primary plus secondary filters (e.g. EN779 G4 plus F8 filters) |
| Level 2 and 3 | Production facility operating on re-circulated plus ambient air, where potential for cross-contamination exists: Primary plus secondary plus tertiary filters (e.g. EN779 G4 plus F8 plus EN1822 H13 filters) |

*Note:* The filter classifications referred to above relate to the EN1822 and EN779 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16).

15.8. Filter classes should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (Different test methods result in a different value for the same filter).

15.9. In selecting filters, the manufacturer should have to consider other factors, such as particularly contaminated ambient conditions. Good pre-filtration extends the life of the more expensive filters downstream.

15.10. Materials for components of an HVAC system should be selected with care so that they do not become the source of contamination. Any component with the potential for liberating particulate or microbial contamination into the air stream should be located upstream of the final filters.

15.11. Ventilation dampers, filters and other services should be designed and positioned so that they are accessible from outside the manufacturing areas (service voids or service corridors) for maintenance purposes.

15.12. Directional airflow within production or packing areas should assist in preventing contamination. Airflows should be planned in conjunction with operator locations, so as to minimize contamination of the product by the operator and also to protect the operator from dust inhalation.

15.13. HVAC air distribution components should be designed, installed and located to prevent contaminants generated within the room from being spread. Supply air diffusers of the high induction type (e.g. those typically used for office-type air- conditioning) should where possible not be used in clean areas where dust is liberated. Air diffusers should be of the non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect. Air should be exhausted from a low level in rooms to help provide a flushing effect.

15.14. Unidirectional airflow (UDAF) should be used to provide product protection by supplying a clean air supply over the product, minimizing the ingress of contaminants from surrounding areas. Where appropriate, the unidirectional airflow should also provide protection to the operator from contamination by the product. Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for the further processing of the product.

15.15. In a weighing booth situation, the aim of the design using UDAF should be to provide

dust containment. A dispensary or weighing booth should be provided with unidirectional airflow for protection of the product and operator. The dust generated

at the weighing station should be extracted through the perforated worktop, thus protecting the operator from dust inhalation and at the same time protecting the product from contamination by the operator by means of the vertical unidirectional airflow stream.

15.16. The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas. Where necessary the velocity may be reduced to prevent inaccuracies during weighing, provided that sufficient airflow is maintained to provide containment.

15.17. The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product. There should be no obstructions in the path of a unidirectional flow air stream that may cause the operator to be exposed to dust.

15.18. The manufacturer should select either vertical or horizontal unidirectional flow or an appropriate airflow pattern to provide the best protection for the particular application.

15.19. Air infiltration of unfiltered air into a pharmaceutical plant should not be the source of contamination. Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure to prevent the escape of harmful products to the outside (such as penicillin and hormones and other hazardous substance), special precautions should be taken. The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structureis well sealed. Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

## Cross-Contamination

15.20. Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another. Correct directional air movement and a pressure cascade system can assist in preventing cross- contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment. The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

15.21. Containment can normally be achieved by application of the displacement concept (low pressure differential, high airflow), or the pressure differential concept (high pressure differential, low airflow), or the physical barrier concept.

15.22. The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used. Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure. The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required. Building structure should be given special attention to accommodate the pressure cascade design. Airtight ceilings and walls, close fitting doors and sealed light fittings should be in place.

15.23. The high pressure differential between the clean and less clean zones should be generated by leakage through the gaps of the closed doors to the cubicle. The pressure differential should be of sufficient magnitude to ensure containment and prevention of

flow reversal, but should not be so high as to create turbulence problems. In considering

room pressure differentials, transient variations, such as machine extract systems, should be taken into consideration. The most widely accepted pressure differential for achieving containment between two adjacent zones is 15 Pa, but pressure differentials of between 5 Pa and 20 Pa may be acceptable. Where the design pressure differential is too low and tolerances are at opposite extremities, the implications of the upper and lower tolerances on containment should be evaluated to ensure the absence of airflow reversal.

15.24. The pressure differential between adjacent rooms could be considered a critical parameter, depending on the outcome of risk analysis. The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, e.g. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tolerance and the second room is at the minimum tolerance.

15.25. Low pressure differentials may be acceptable when airlocks (pressure sinks or pressure bubbles) are used.

15.26. The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis. Manual control systems, where used, should be set up during commissioning and should not change unless other system conditions change.

15.27. Airlocks can be important components in setting up and maintaining pressure cascade systems. Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:

a. **Cascade airlock:** higher pressure on one side of the airlock and lower pressure on the other (for an example, see Fig. A3.11);
b. **Sink airlock**: lower pressure inside the airlock and higher pressure on both outer sides (for an example, see Fig. A3.12);
c. **Bubble airlock:** higher pressure inside the airlock and lower pressure on both outer sides (for an example, see Fig. A3.13).

Fig. A3.10: Examples of pressure cascades

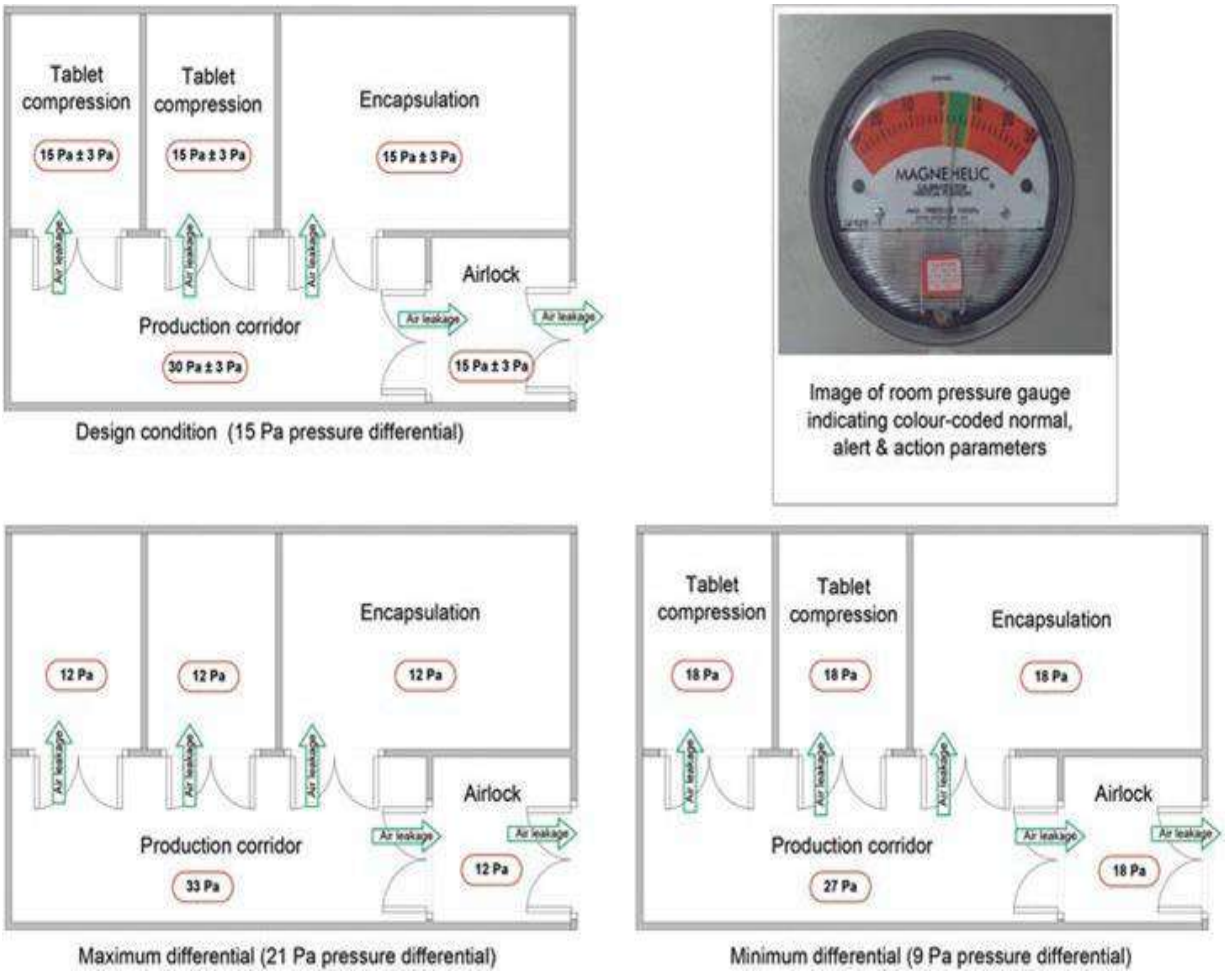



Fig. A3.11

Example of a cascade airlock: in most cases, the internal pressure of the airlock is not critical; the pressure differential between the two outer sides is the important criterion

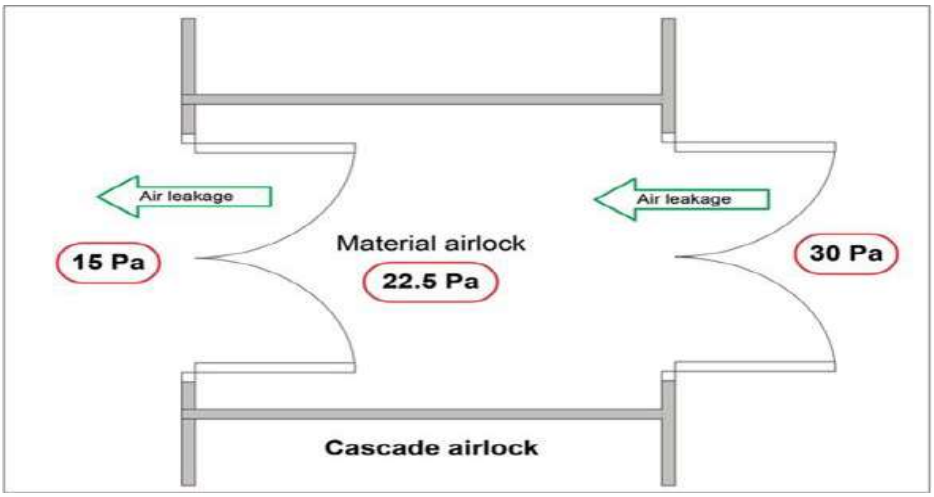


Fig. A3.12

***Example of a sink airlock***

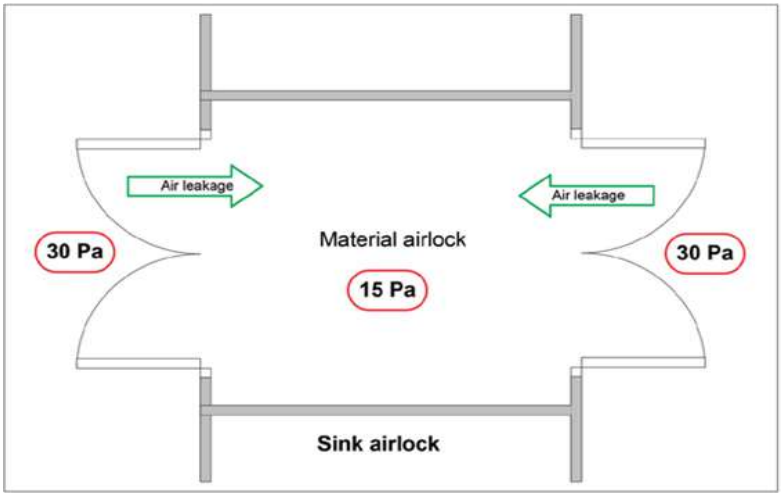
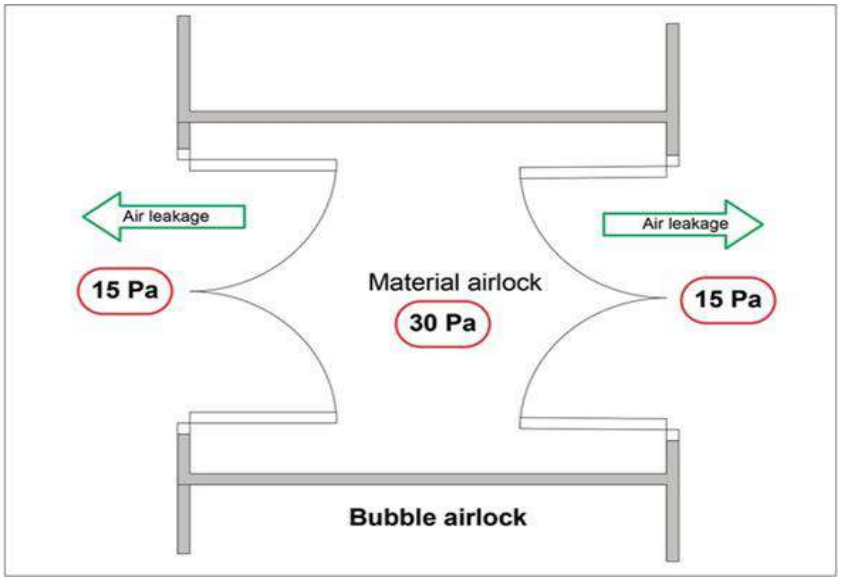



Fig. A3.13

***Example of a bubble airlock***




– *Note: The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be the pressure differential from room to room.*

15.28. Additional controls should be identified through risk identification and risk assessment. For example, where possible, personnel should not move between different areas during production (such as compression rooms and in process control laboratories), unless there is no risk of contamination of other areas. Personnel often become sources of contamination, as they may carry dust from one area to another. Controls may include airlocks or gowning procedures.

15.29. Doors should open to the high-pressure side, and be provided with self-closers. Door closer springs, if used, should be designed to hold the door closed and prevent the pressure differential from pushing the door open. Sliding doors are not recommended.
15.30. Central dust extraction systems should be interlocked with the appropriate air handling systems, to ensure that they operate simultaneously.
15.31. Room pressure imbalance between adjacent cubicles which are linked by common dust extraction ducting should be prevented.
15.32. Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting (this would normally occur only if the dust extraction system was inoperative).

## Temperature and Relative Humidity

15.33. Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products, and to provide a comfortable environment for the operator where necessary. Maximum and minimum room temperatures and relative humidity should be established.
15.34. Temperature conditions should be adjusted to suit the needs of the operators while wearing their protective clothing. The operating band, or tolerance, between the acceptable minimum and maximum temperatures should not be made too close.
15.35. Cubicles, or suites, in which products requiring low humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher humidity by means of suitable airlocks.
15.36. Precautions should be taken to prevent moisture migration that increases the load on the HVAC system. Humidity control should be achieved by removing moisture from the air, or adding moisture to the air, as relevant.
15.37. Dehumidification (moisture removal) may be achieved by means of either refrigerated dehumidifiers or chemical dehumidifiers. Appropriate cooling media for dehumidification such as low temperature chilled water/glycol mixture or refrigerant should be used.
15.38. Humidifiers should be avoided if possible as they may become a source of contamination (e.g. microbiological growth). Where humidification is required, this should be achieved by appropriate means such as the injection of steam into the air stream. A product-contamination assessment should be done to determine whether pure or clean steam is required for the purposes of humidification.
15.39. Where steam humidifiers are used, chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system.
15.40. Humidification systems should be well drained. No condensate should accumulate in air-handling systems.
15.41. Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used because of the potential risk of microbial contamination.
15.42. Duct material in the vicinity of the humidifier should not add contaminants to air that will not be filtered downstream.
15.43. Air filters should not be installed immediately downstream of humidifiers.
15.44. Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components.
15.45. When specifying relative humidity, the associated temperature should also bespecified.
15.46. Chemical driers using silica gel or lithium chloride are acceptable, provided that they do not become sources of contamination.

## Dust Control

15.47. Wherever possible, the dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where the dust is generated, should be employed. Point-of-use extraction should be either in the form ofa fixed high velocity extraction point or an articulated arm with movable hood or a fixed extraction hood.

15.48. Dust extraction ducting should be designed with sufficient transfer velocity to ensure that dust is carried away, and does not settle in the ducting. The required transfer velocity should be determined: it is dependent on the density of the dust (the denser the dust, the higher the transfer velocity should be, e.g. 15–20 m/s).

15.49. Airflow direction should be carefully chosen, to ensure that the operator does not contaminate the product, and so that the operator is not put at risk by the product. Dust-related hazards to which the operators may be subjected should be assessed. An analysis of the type of dust and toxicity thereof should be done and the airflow direction determined accordingly.

15.50. Point extraction alone is usually not sufficient to capture all of the contaminants, and general directional airflow should be used to assist in removing dust and vapours from the room. Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers and extracted from the room at low level to help give a flushing effect in the room.

15.51. The low-level extraction should assist in drawing air downwards and away from the operator's face. The extract grilles should be positioned strategically to draw air away from the operator, but at the same time to prevent the operator from contaminating the product.

15.52. When planning the system for the extraction of vapours, the density of the vapour should be taken into account. If the vapour is lighter than air, the extract grilles should be at a high level, or possibly at both high and low levels.

15.53. When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

15.54. When working with exposed products such as hormones or highly potent products, operators should wear totally enclosed garments. Operators should also be equipped with an air-breathing system that provides a supply of filtered and conditioned air. The air supply to this type of breathing apparatus should normally be through an air compressor. Filtration, temperature and humidity need to be controlled to ensure operator safety and comfort.

15.55. The rates at which fresh air is supplied (NLT 20$m^3$/min) to the facility should provide operators with an acceptable level of comfort and safety and also to remove odours or fumes. The rate of fresh airflow should also be determined by leakage from the building, for pressure control purposes.

## Protection from the Environment

### General

15.56. Protection of the environment should be compliant with relevant local and national legislationand standards.

15.57. Exhaust air discharge points on pharmaceutical equipment and facilities, such as from

fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.

15.58. Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN779 filter standards.

15.59. Where harmful substances such as penicillin, hormones, toxic powders and enzymes are manufactured, the final filters on the dust exhaust system should be HEPA filters with at least an H12 classification according to EN1822 filter standards, as appropriate.

15.60. For exhaust systems where the discharge contaminant is considered particularly hazardous, it may be necessary to install two banks of HEPA filters in series, to provide additional protection should the first filter fail.

15.61. When handling hazardous compounds, safe-change filter housings, also called "bag- in-bag-out" filters, should be used.

15.62. All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading. Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

15.63. Exhaust filters should be monitored regularly to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in contamination of the ambient air.

15.64. Where reverse-pulse dust collectors are used for removing dust from dust extraction systems, they should usually be equipped with cartridge filters containing a compressed air lance, and be capable of continuous operation without interrupting the airflow. Alternative types of dust collectors (such as those operating with a mechanical shaker, requiring that the fan be switched off when the mechanical shaker is activated) should be used in such a manner that there is no risk of cross- contamination. There should be no disruption of airflow during a production run as the loss of airflow could disrupt the pressure cascade.

15.65. Mechanical-shaker dust collectors should not be used for applications where continuous airflow is required.

15.66. When wet scrubbers are used, the dust-slurry should be removed by a suitable drainage system.

15.67. The quality of the exhaust air should be determined to see whether the filtration efficiency is adequate with all types of dust collectors and wet scrubbers.

15.68. Where necessary, additional filtration may be provided downstream of the dust collector.

## Vapour and Fume Removal

15.69. The systems for fume, dust and effluent control should be designed, installed and operated in such a manner that they do not become possible sources of contamination or cross-contamination, e.g. an exhaust-air discharge point located close to the HVAC system fresh air inlet.

15.70. Fumes should be removed by means of wet scrubbers or dry chemical scrubbers (deep-bed scrubbers). Wet scrubbers for fume removal normally require the additionof various chemicals to the water to increase the adsorption efficiency.

15.71. Deep-bed scrubbers should be designed with activated carbon filters or granular chemical adsorption media. The chemical media for deep-bed scrubbers should be specific to the effluent being treated.

15.72. The type and quantity of the vapours to be removed should be known to enable the appropriate filter media, as well as the volume of media required to be determined.

## HVAC System and Component

### Principle

The required degree of air cleanliness in most OSD manufacturing facilities can normally be achieved without the use of high-efficiency particulate air (HEPA) filters provided the air is not re-circulated.

### General

15.73. There should be no failure of a supply air fan, return air fan, exhaust air fan or dust extract system fan. Failure can cause a system imbalance, resulting in a pressure cascade malfunction with a resultant airflow reversal.

15.74. Air should be dried with a chemical drier (e.g. a rotating desiccant wheel which is continuously regenerated by means of passing hot air through one segment of the wheel).

15.75. Possible additional components that may be required should be considered depending on the climatic conditions and locations. These may include items such as:

a. frost coils on fresh air inlets in very cold climates to preheat the air;
b. snow eliminators to prevent snow entering air inlets and blocking airflow;
c. dust eliminators on air inlets in arid and dusty locations;
d. moisture eliminators in humid areas with high rainfall; and
e. fresh air pre-cooling coils for very hot or humid climates.

15.76. Appropriate alarm systems should be in place to alert personnel if a critical fan fails.

15.77. Low-level return or exhaust air grilles are usually preferred. However, where this is not possible, a higher air change rate may be needed to achieve a specified clean area classification, e.g. where ceiling return air grilles are used.

### Design of HVAC systems and components

15.78. The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in- process materials or products, processing, and movement of materials, products and personnel.

15.79. The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be specified, based on need. Manufacturers should determine and define limits for these. These should be realistic, appropriate, scientifically justifiable at rest, in operation, and as built at the time of design.

15.80. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination.

15.81. Other aspects, such as the number of AHUs, dust-collecting or dust- extraction systems, the need for recirculation of air, percentage of fresh air (in the case of recirculated air) and the level of filtration of air should be defined by the manufacturer when considering the design of the facility and activities in different areas and rooms.

15.82. Manufacturers should maintain schematic drawings of the HVAC system, AHUs and components. These should reflect the initial design and installation, as well as the current

situation. Changes made during the life-cycle of the system should be reflected in change-control records and qualification protocols and reports, as appropriate. The components selected in an HVAC system should be of sufficient capacity to ensure that the design objectives are met (e.g. for heating, cooling, humidification, dehumidification, airflow volumes), considering impacting factors, such as loss of air due to leakage and seasonal variations. Materials for construction of components, and their placement, should be such that these do not become the source of contamination. For example, components should not shed particles and the sequence of components should be logical; for example, filters should be placed in such a manner that any possible contaminants generated in the system can be retained by filters and not be introduced into the production area.

15.83. To prevent contamination of areas, components such as ventilation dampers, filters and other services should be accessible from outside the manufacturing areas (such as service corridors). The overall design should be such that there is no possibility of undesired, unfiltered air or contaminants entering manufacturing areas.

15.84. Containment

Manufacturers should ensure that appropriate measures are taken to contain product dust in a manufacturing area, thus preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, it may be advisable to have airlocks or pass-through hatches between rooms or areas. In addition, sufficient dilution, pressure differentials (recommended minimum values of 5 Pa) and airflow directions can further support containment in an area.

15.85. Cleanliness

Areas should be maintained at the defined levels of cleanliness and classifications. The HVAC system can support this through, for example, appropriate levels of filtration of air, dilution and dust removal. Equipment, containers, personnel and other related components should be appropriately located or placed in areas so as not to obstruct airflow and the effectiveness of the HVAC system. Recontamination should be prevented by ensuring that movement of material and personnel is within the same area classification and not back and forth between areas of different classification. Where such back-and- forth movement is unavoidable, appropriate controls should be identified and implemented, to ensure that moving from a higher class to a lower-classified area and back to a higher-classified area will not result in contaminants being brought into the cleaner classified area.

15.86. Automated monitoring systems

The performance of the HVAC system achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow and pressure differential should be carefully controlled and monitored. This is to ensure that there is no departure from these limits during manufacturing. Monitoring systems should be in place to ensure that the system operates within its design limits. Manual or automated (computerized) systems may be used. Automated monitoring systems may provide possibilities for ongoing monitoring with better assurance of compliance with the defined limits. Where these automated systems are considered good practice (GXP) systems, these should be appropriately validated. The scope and extent of validation of the computerized system should be determined, justifiable and appropriately executed. This includes, but is not limited to, access and privileges to the software, setting of limits, monitoring and acknowledging alarms, audit trails, controls, and reporting.

15.87. Switching off air-handling units

It is recommended that the HVAC system be operational on an ongoing basis. Where a manufacturer decides to use energy-saving modes or switch some selected AHUs off at specified intervals, such as overnight, at weekends or for extended periods of time, care should be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard operating procedures, records and validation. This includes procedures and records for the start-up and shutdown sequence of AHUs.

## Full fresh air systems and recirculation systems

15.88. Manufacturers may select to have full fresh air systems (for an example, see Fig. A2.8) or recirculate treated air supplied to production areas (in a full fresh air system, no air is recirculated; in recirculation systems, a defined percentage of the air is recirculated).

15.89. Manufacturers using recirculation systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, as required by national and international standards. This volume of air should be verified during qualification.

15.90. There should be no risk of contamination or cross-contamination (including by fumes and volatiles) due to recirculation of air.

15.91. Depending on the airborne contaminants in the return-air system, it may be acceptable to use re-circulated air, provided that HEPA filters are installed in the supply air stream to remove contaminants and thus prevent cross-contamination. The HEPA filters for this application should have an EN1822 classification of H13.

15.92. HEPA filters may not be required for OSD where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.

15.93. Recirculation of air from areas where pharmaceutical dust is not generated such as secondary packing may not require HEPA filters in the system.

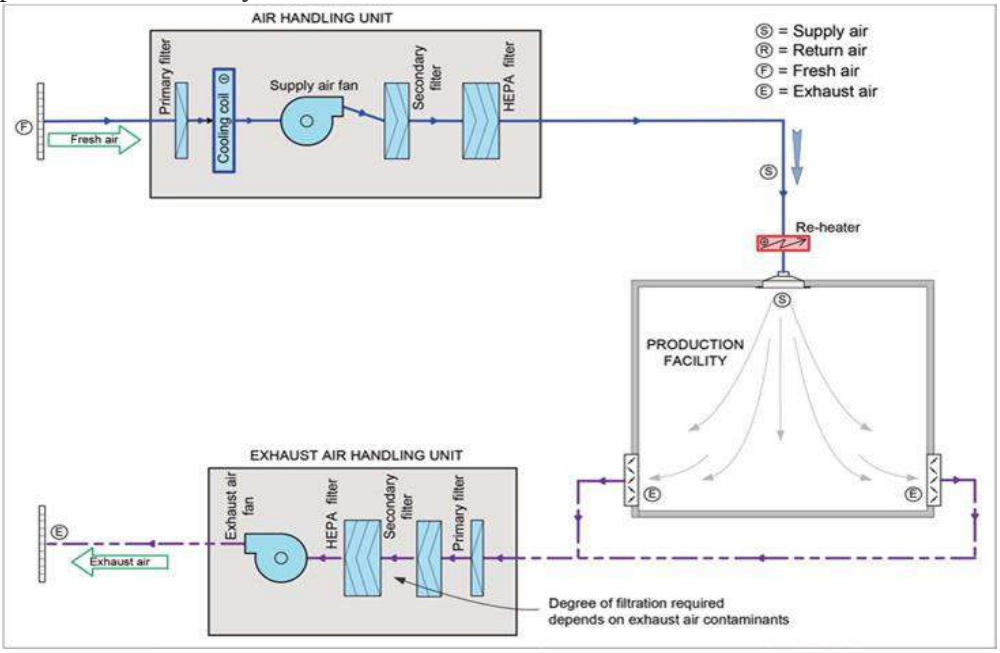
15.94. HEPA filters may be located in the air-handling unit or placed terminally.

15.95. Air containing dust from highly toxic processes should never be re-circulated to the HVAC system.

15.96. Full (100% fresh) air would normally be used in a facility dealing with toxic products, where recirculation of air with contaminants should be avoided. The required degree of filtration of the exhaust air depends on the exhaust air contaminants and environmental regulations.

15.97. In both scenarios, appropriate levels of filtration should be applied, to prevent contamination and cross-contamination. Manufacturers should ensure that when high-efficiency particulate air (HEPA) filters are used, these are appropriately installed, not damaged and thus suitable for the intended use.

Fig. A3.14
Example of a full fresh air system




## 15.98. Air filtration, airflow direction and pressure differentials

15.98.1. Manufacturers should determine which classes of filters should be used in ensuring that contaminants from outside are not introduced into manufacturing areas and that where recirculation systems are used, filtration of recirculated air is carried out effectively, to ensure that there is no risk of cross-contamination.

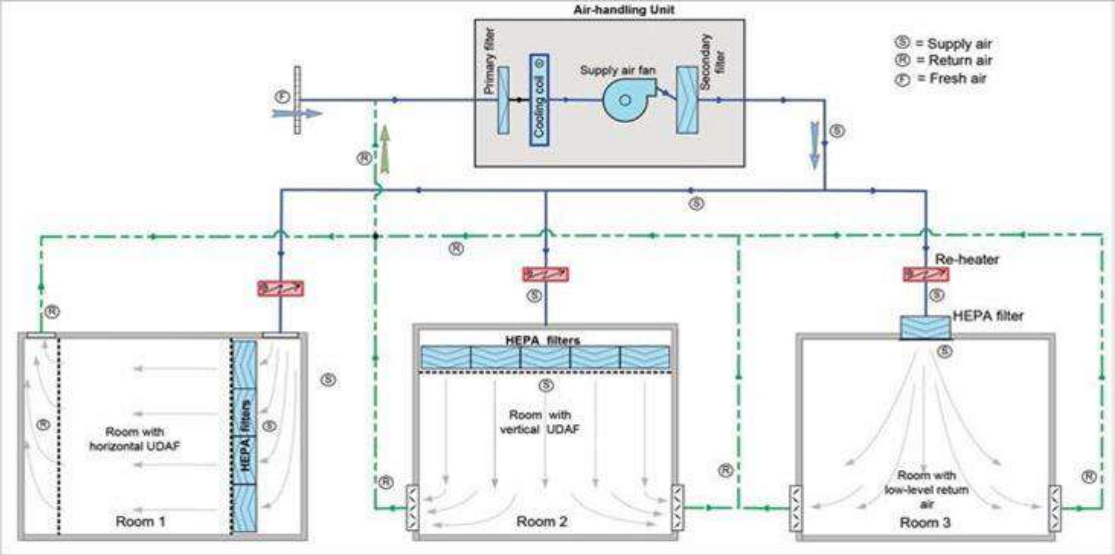
15.98.2. Where different products are manufactured in different rooms in the same facility at the same time, appropriate controls should be in place to ensure containment and prevention of contamination and cross-contamination.

15.98.3. When a manufacturer chooses to install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.

15.98.4. The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour. Manufacturers should also establish how much time it takes for a room that is out of its classification to return within the specified class. This is often referred to as clean up or recovery time. A guidance time period for clean-up or recovery is about 15–20 minutes.

15.98.5. Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate air flow directions in an area. Fig. A3.15 is a schematic diagram of an example of an air-handling system serving rooms with horizontal directional flow, vertical directional flow and turbulent flow, for rooms 1, 2 and 3, respectively. In these rooms, the HEPA filters are indicated to have been placed terminally mounted in the rooms and not in the AHU. Whenever HEPA filters are terminally mounted, it can assist with preventing cross-contamination from room to room in the event of a fan failure.

Fig. A3.15
Example of horizontal airflow, vertical flow and turbulent flow




## Commissioning, Qualification and maintenance of HVAC system

15.99. Commissioning should include the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that it meets all the requirements, as specified in theuser requirement specification (URS), and capacities as specified by the designer or developer. The installation records of the system should provide documented evidence of all measured capacities of the system.

15.100. The data should include items such as the design and measurement figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

15.101. Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation. Training should be provided to personnel after installation of the system, and should include operation and maintenance. Commissioning should be a precursor to system qualification and process validation.

15.102. Based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include: temperature, relative humidity, supply air quantities for all diffusers, return air or exhaust air quantities, room air change rates, room pressures (pressure differentials), room airflow patterns, unidirectional flow velocities, containment system velocities, HEPA filter penetration tests, room particle counts, room clean-up rates, microbiological air and surface counts where appropriate, operation of de-dusting, warning/alarm systems where applicable ( see table.

15.103. Periodic re-qualification of parameters should be done at regular intervals, e.g. annually. Re-qualification should also be done when any change, which could affect system performance, takes place.

15.104. There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept. Maintenance personnel should receive appropriate training. Maintenance activities should normally be scheduled to take place outside production hours, and any system stoppage should be assessed with a view to the possible need for re-qualification of an area as a result of an interruptionof the service.

## ANNEX I- MANUFACTURE OF STERILE MEDICINAL PRODUCTS PRINCIPLE

The manufacture of sterile products covers a wide range of sterile product types (such as active substances, excipients, primary packaging materials and finished dosage forms), packed sizes (single unit and multiple units), processes (from highly automated systems to manual processes) and technologies (for example, biotechnology, small molecule manufacturing and closed systems). This guideline provides general guidance that should be used in the design and control of premises, equipment, utilities, systems and procedures used for the manufacture of all sterile products. The principles of quality risk management should be applied to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

### General Principle

1. The manufacture of sterile products is subject to specific requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. As a minimum, the following areas should be considered:
    i. Premises, equipment and process should be appropriately designed, qualified and validated and, where applicable, be subjected to ongoing verification according to the relevant sections of the good manufacturing practices (GMP) guide. The use of appropriate technologies (such as restricted access barrier systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential sources of endotoxin/pyrogen, particulate and microbial contamination, such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.
    ii. Personnel should have adequate qualifications, experience, and training. They should behave in a manner that ensures the protection of sterile product during the manufacturing, packaging and distribution processes.
    iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge and experience.
    iv. Raw materials and packaging materials should be adequately controlled and tested for bioburden and endotoxin/pyrogen. These materials should meet their specification and should be suitable for use.
2. Processes, equipment, facilities and manufacturing activities should be managed in accordance with the principles of quality risk management to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale and scientific justification. Quality risk management principles should cover the appropriate design of the facility, equipment and processes, as well as well designed procedures, and the application of monitoring systems that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.
3. A Contamination control strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural,

technical and organizational) and monitoring measures employed to manage risks to medicinal product quality. The combined strategy of the CCS should provide robust assurance of contamination prevention. The CCS should be reviewed periodically and, where appropriate, updated to drive continual improvement. Its effectiveness should be reviewed as part of the periodic management review process. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.

4. Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources should include a series of interrelated events and measures. These should be assessed and controlled and their effectiveness monitored individually and collectively.
5. The manufacturer should take all necessary steps and precautions to ensure the sterility of the products manufactured. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product testing.

6. Four grades of cleanrooms or zones are normally used for the manufacture of sterile products.

   **Grade A.** This is the critical zone for high-risk operations (for example, aseptic processing line, filling zone, stopper bowl, open primary packaging, or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localized airflow protection, such as unidirectional airflow work stations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (for example, without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

   **Grade B.** For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Where applicable, air pressure differential between grade B and an adjacent area should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used.

   **Grades C and D**. These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation or filling of terminally, sterilized products (see section 8 for specific details on terminal sterilization activities).

## Clean Area Classification

1. Clean rooms and clean air devices should be classified in accordance with EN/ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the following table:

Maximum permitted total particle concentration for classification

| Grade | Maximum limits for total particle ≥ 0.5 µm/m³ | | Maximum limits for total particle ≥ 5 µm/m³ | |
|---|---|---|---|---|
| | At rest | In operation | At rest | In operation |
| A | 3 520 | 3 520 | Not specified[a] | Not specified[a] |
| B | 3 520 | 352 000 | Not specified[a] | 2 930 |
| C | 352 000 | 3 520 000 | 2 930 | 29 300 |
| D | 3 520 000 | Not predetermined[b] | 29 300 | Not predetermined[b] |

a Classification including 5 µm particles may be considered where indicated by the CCS or historical trends.
b For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

2. Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0µm in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.
3. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

## Environmental Monitoring

4. Clean rooms and clean air devices should be routinely monitored in operation, the monitoring locations based on a formal risk analysis study, and the results obtained during the classification of rooms and/or clean air devices.
5. For grade A, particle monitoring should be undertaken for the full durationof critical processing, including equipment assembly.
6. The grade A area should be monitored continuously (for particles ≥ 0.5 and ≥ 5 µm) and with a suitable sample flow rate (at least 28 litres per minute)so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms, including the consideration of additional microbial monitoring.
7. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.
8. The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations

posing the highest risk of contamination of the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.

9. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.
10. In Grade A and B zones, the monitoring of the ≥5.0μ particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation. The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period of 15-20 minutes in an unmanned state after completion of operations.
11. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean up period" should be attained.
12. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard. Examples of operations to be carried out in the various grades are given in the table below:

| Grade | Examples of operations for terminally sterilized products |
|---|---|
| A | Filling of products, when unusually at risk |
| C | Preparation of solution, when unusually at risk. Filling of products |
| D | Preparation of solution and components for subsequent filling |

13. Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (for example, using swabsand contact plates). The method of sampling used should be justified withinthe CCS and should be demonstrated not to have a detrimental impact ongrade A and B airflow patterns. Cleanroom and equipment surfaces shouldbe monitored at the end of an operation,
14. Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (for example, post disinfection, prior to start of manufacturing, upon completion of the batch and after a shutdown period), and in associated rooms that have not been used in order to detect potential incidents of contamination that may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (such as cleaning and disinfection)

15. Continuous viable air monitoring in grade A (for example, air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be detected and captured to alert any risk caused.

16. A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where the monitoring of gloves is performed after critical interventions, outer gloves should be replaced prior to continuation of activity. Where the monitoring of gowns is required after critical interventions, each gown should be replaced before further activity in the cleanroom.

17. Microbial monitoring of personnel in the grade A and B areas should be performed. Where operations are manual in nature (such as aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.

18. Action limits for viable particle contamination are shown in the table below:

**Maximum action limits for viable particle contamination**

| Grade | Air sample CFU/m3 | Settle plates (diam. 90 mm)CFU/4 hours[a] | Contact plates (diam. 55 mm) CFU/plate[b] | Glove print, incl. 5 fingers on both handsCFU/glove |
|---|---|---|---|---|
| A | | No growth[c] | | |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | – |
| D | 200 | 100 | 50 | – |

CFU = colony-forming unit.

a Settle plates should be exposed for the duration of operations and changed as required, or after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

**Note 1:** All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

**Note 2:** Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

**Note 3**: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table.6 should apply.

**Note 4:** Sampling methods should not pose a risk of contamination to the manufacturing operations.

19. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

## Barrier/Isolator Technology

20. The utilization of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realized. Isolators are constructed of various materialsmore or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.
21. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.
22. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.
23. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.
24. Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.

## Blow/Fill/Seal Technology

25. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised should be installed in at least a grade D environment.
26. Because of this special technology particular attention should be paid to, at least the following:
    a. equipment design and qualification
    b. validation and reproducibility of cleaning-in-place and sterilisation-in-place
    c. background clean room environment in which the equipment is located
    d. operator training and clothing
    e. interventions in the critical zone of the equipment including any asepticassembly prior to the commencement of filling.

## Terminally Sterilized Products

27. Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/ pyrogen and particle contamination, so that the product is suitable for sterilization. Where the product is at a high or unusual risk of microbial contamination (for example, the product actively supports microbial growth and must be held for long periods before filling, or the

product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. The preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilization.

28. Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.
29. The filling of products for terminal sterilization should be carried out in at least a grade C environment.
30. Where the CCS identifies that the product is at an unusual risk of contamination from the environment – for example, when the filling operation is slow or when the containers are wide necked or are necessarily exposed for more than a few seconds before closing – then the product should be filled in grade A with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.
31. The processing of the bulk solution should include a filtration step with a microorganism-retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers. The maximum permissible time between preparation and filling should be defined.

## Aseptic Preparation and Processing

32. The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.
33. Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.
34. Where possible, the use of equipment such as RABS, isolators or other systems should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (for example, dry heat tunnel, automated lyophilizer loading, sterilization in place).
35. Examples of operations to be carried out in the various environmental grades are given in Table.

Table Examples of operations and grades for aseptic preparation and processing operations

| Grade | Operation |
|---|---|
| Grade A | • Aseptic assembly of filling equipment<br>• Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing grade filter; these connections should be sterilized by steam-in-place whenever possible<br>• Aseptic compounding and mixing |

| | |
|---|---|
| | • Replenishment of sterile bulk product, containers and closures<br>• Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers<br>• Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped<br>• Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials<br>• Loading of a lyophilizer |
| Grade B | • Background support for grade A (when not in an isolator)<br>• Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A |
| Grade C | • Preparation of solutions to be filtered, including sampling and dispensing |
| Grade D | • Cleaning of equipment<br>• Handling of components, equipment and accessories after cleaning<br>• Assembly under high-efficiency particulate air (HEPA)-filtered airflow of cleaned components, equipment and accessories prior to sterilization<br>• Assembly of closed and sterilized SUS using intrinsic sterile connection devices |

36. For sterile products where the final formulation cannot be filtered, the following should be considered:
    i. All product and component contact equipment should be sterilized prior to use.
    ii. All raw materials or intermediates should be sterilized and aseptically added.
    iii. Bulk solutions or intermediates should be sterilized.

37. The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background.
38. Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilizing grade filter) or terminally sterilized.
39. Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilized in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.
40. Aseptic connections should be appropriately assessed and their effectiveness verified (for requirements regarding intrinsic sterile connection devices).
41. Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized using engineering design solutions such as preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be preassembled and sterilized in place.
42. There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production. Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively

minimized. The process of designing interventions should include the consideration of any impact on airflows and critical surfaces and products. Operators should use engineering solutions whenever possible to minimize incursion during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and aseptic process simulation and should be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorization of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.

43. Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved.
44. The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:
    i. the holding time between equipment, component, and container cleaning, drying and sterilization;
    ii. the holding time for sterilized equipment, components, and containers before use and during filling or assembly;
    iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;
    iv. the time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process (there should be a maximum permissible time defined for each product that takes into account its composition and the prescribed method of storage);
    v. the holding time for sterilized product prior to filling;
    vi. the aseptic processing time;
    vii. the filling time.
45. Personnel (independent from the aseptic operation) with specific expertise in aseptic processing to verify the correct performance of operations, including operator behaviour in the cleanroom, and to address inappropriate practices if detected should monitor aseptic operations (including aseptic process simulation) on a regular basis. Records should be maintained.

## Personnel

46. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
47. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not

received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

48. Personnel, including those performing cleaning, maintenance and monitoring and those that access cleanrooms, should receive regular training and undergo gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene (with a specific focus on cleanroom practices), contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms or intervening into grade A), and the potential safety implications for the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.

49. The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment using monitoring locations such as gloved fingers, forearms, chest and hood (face mask and forehead). Unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.

50. Unqualified persons should not enter grade B cleanrooms or grade A when in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified persons are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified persons during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.

51. There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on specified aspects, including ongoing assessment or identification of an adverse trend from the personnel monitoring programme or implication in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful APS.

52. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.

53. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition, which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated qualified person.

54. Wristwatches, make-up and jewellery should not be worn in clean areas.

55. Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.

56. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from

contamination.

57. The description of clothing required for each grade is given below:
    a. Grade B (including access or interventions into grade A). Appropriate garments that are dedicated for use under a sterilized suit should be worn before gowning appropriately sterilized, non-powdered, rubber or plastic gloves should be worn while donning the sterilized garments. Sterile headgear should enclose all hair (including facial hair) and, where separate from the rest of the gown, should be tucked into the neck of the sterile suit. A sterile face mask and sterile eye coverings (such as goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. The appropriate sterilized footwear (such as overboots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres and other particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.
    b. Grade C. Hair, beards and moustaches should be covered. A single- or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.
    c. Grade D. Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. The appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.
    d. Additional gowning, including gloves and a face mask, may be required in grade C and D areas when performing activities considered to be a contamination risk, as defined by the CCS.

58. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

59. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

## Premises

60. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

61. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

62. False ceilings should be sealed to prevent contamination from the space above them.
63. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.
64. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.
65. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at- rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.
66. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
67. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals. Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.
68. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk.
69. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

## Disinfection

70. The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, cleaning to remove surface contamination should be performed prior to disinfection. Cleaning programmes should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (for example, organisms resistant to the disinfection regime currently in use).
71. The disinfection process should be validated. Validation studies should demonstrate

the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.

72. Disinfectants and detergents used in grade A and B areas should be sterile. Disinfectants used in grade C and D areas may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted or prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination, and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned (and sterilized, where applicable) containers and should only be stored for the defined period. If the disinfectants and detergents are supplied ready-made, then results from certificates of analysis or conformance can be accepted, subject to successful completion of the appropriate vendor qualification.

73. Where fumigation or vapour disinfection (for example, vapour phase hydrogen peroxide) of cleanrooms and associated surfaces is used, the effectiveness of the fumigation agent and dispersion system should be validated.

## Equipment

74. A detailed written description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification documentation and be kept up to date.

75. Equipment monitoring requirements should be defined in user requirements specifications during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).

76. As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel and generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be performed where appropriate. If sterilization of equipment is required, it should be carried out, wherever possible, after complete reassembly.

77. The validated cleaning procedure should be able to:
    i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used;
    ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

78. For aseptic processes, direct and indirect product contact parts should be sterilized. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product but may come into contact with other sterilized surfaces, the sterility of which is critical to the overall product sterility (for example, sterilized items such as stopper bowls and guides, and sterilized components).

79. All equipment, such as sterilizers, air handling systems (including air filtration systems) and water systems, should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance or repairs, their return to use should be

approved.

80. Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.
81. A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (for example, in a sterilizing tunnel).
82. Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1 m unless justified, and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.

## Utilities

83. The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined through risk assessment and documented as part of the CCS.
84. In general, higher-risk utilities are those that:

    i. directly contact product (for example, water for washing and rinsing, gases and steam for sterilization);
    ii. contact materials that will ultimately become part of the product;
    iii. contact surfaces that come into contact with the product;
    iv. Otherwise directly impact the product.

85. Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner that ensures that the utility system functions as expected.
86. Results for critical parameters and critical quality attributes of high-risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
87. Records of utility system installation should be maintained throughout the system's life cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as:
    i. pipeline flow direction, slope, diameter and length
    ii. tank and vessel details
    iii. valves, filters, drains, sampling points and user points.
88. Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes

## Aspetic process Simulation

89. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.
90. Periodic verification of the effectiveness of the controls in place for aseptic processing should include an aseptic process simulation (APS) (also known as media fill) using a sterile nutrient medium or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the

aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the PQS and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient medium or surrogate should be made based on the ability of the medium or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination (for example, aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

91. The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

i. The APS should cover all aseptic operations performed subsequent to the sterilization and decontamination cycles of materials utilized in the process to the point where the container is sealed.

ii. For non-filterable formulations, any additional aseptic steps should be covered.

iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.

iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.

v. Separate simulations of individual unit operations (for example, processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.

vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain, including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst-case operating parameters.

vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable:

- the use of air to break vacuum instead of nitrogen or other process gases;
- replicating the maximum interval between sterilization of the lyophilizer and its use;
- replicating the maximum period of time between filtration and lyophilization;
- quantitative aspects of worst-case situations, for example, loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

92. APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic

process may occur in, and after any significant modification to operational practices, facilities, services or equipment that are assessed to have an impact on the sterility assurance of the product (such as modification to the HVAC system or equipment, changes to process, number of shifts and numbers of personnel, or major facility shutdown). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shutdown, before long periods of inactivity or before decommissioning or relocation of a line.

93. The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10 000 units should be filled. For small batches (for example, those under 5000 units), the number of containers for APS should at least equal the size of the production batch.

94. Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the medium with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those that have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production standard operating procedures clearly specify that units must be removed under the same circumstances (that is, type of intervention, line location and specific number of units removed). In no case should more units be removed during an APS intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic set-up or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

95. Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (such as amber glass or opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.

96. Filled APS units should be incubated without delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.

97. On completion of incubation:

i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.

ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

98. The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken.

i. An investigation should be undertaken to determine the most probable root causes.

ii. Appropriate corrective measures should be determined and implemented.

iii. A sufficient number of successful, consecutive repeat APS (normally a minimum of three) should be conducted in order to demonstrate that the process has been returned to a state of control.

iv. A prompt review should be made of all appropriate records relating to aseptic production since the last successful APS:

- The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS.
- All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.

v. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred.

vi. Where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken.

vii. Production should resume only after completion of successful revalidation

99. All APS runs should be fully documented and include a reconciliation of units processed (such as units filled, incubated and not incubated). The justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data, as well as other testing data, should be recorded in the APS batch record.

100. An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.

101. An aseptic process should be subject to a repeat of the initial validation when:

i. the specific aseptic process has not been in operation for an extended period of time;

ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.

102. Routine production, after completion of the APS, should only commence after validated procedures have been completed in accordance with the CCS, to ensure that there is no risk to the product.

## Sterilization

103. All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of official Pharmacopoeia or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilization is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.
104. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
105. For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
106. Validated loading patterns should be established for all sterilisation processes.
107. Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.
108. There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch numberand an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.
109. Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

## Sterilization by Heat

110. Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.
111. Chemical or biological indicators may also be used, but should not take the place of physical measurements.
112. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.
113. After the high temperature phase of a heat sterilisation cycle, precautions shouldbe taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.

## Sterilization by Moist Heat

114. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.
115. The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.
116. Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

## Sterilization by Dry Heat

117. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

## Sterilization by Radiation

118. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.
119. During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
120. Biological indicators may be used as an additional control
121. Validation procedures should ensure that the effects of variations in density of the packages are considered.
122. Materials handling procedures should prevent mix-up between irradiated and non-

irradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.

123. The total radiation dose should be administered within a predetermined time span.

## Sterilization with Ethylene Oxide

124. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

125. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

126. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this mshould be balanced against the opposing need to minimise the time before sterilisation.

127. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

128. For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

129. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

## Sterilization by Filtration

130. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

131. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised microorganism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

132. Fibre-shedding characteristics of filters should be minimal.

133. The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined

during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

134. The same filter should not be used for more than one working day unless such use has been validated.

135. The filter should not affect the product by removal of ingredients from it or by release of substances into it.

## Finishing of Sterile Products

136. Open primary packaging containers should be maintained under grade A conditions with the appropriate background.

137. Filled containers should be closed by appropriately validated methods.

138. Where fusion for example, blow-fill-seal (BFS), form-fill-seal (FFS), or small- or large-volume parenteral bags, glass, close filled containers or plastic ampoules – the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small- volume containers (≤ 100 mL) closed by fusion should be subject to 100% integrity testing using validated methods. For large-volume containers (> 100 mL) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. Visual inspection is not an acceptable integrity test method.

139. Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier qualification, packaging component specifications and process knowledge.

140. Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate predetermined period prior to certification and release and during shelf life.

141. The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively affect the integrity of the container (for example, by decompression or extreme temperatures).

142. Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination, such as locating the equipment at a physically separate station equipped with adequate air extraction, and should be taken.

143. Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.

144. Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately, qualified, automated methods for stopper height detection should be in place.
145. Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination.
146. All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects.
147. When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually.
148. Where automated methods of inspection are used, the process should be validated to detect known defects (which may affect product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start-up and at regular intervals throughout the batch.
149. The results of the inspection should be recorded and defect types and numbers trended. The reject levels for the various defect types should also be trended based on statistical principles. The impact to the product on the market should be assessed as part of the investigation when adverse trends are observed.

## Quality Control

150. There should be a sufficient number of personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation needed to assess the impact of microbiologically linked events on the quality and safety of the sterile product.
151. Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring or by the CCS.
152. The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilizing grade filter or the terminal sterilization process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst-case scenario (for example, at the end of hold time). Where overkill sterilization parameters are set for terminally sterilized products, bioburden should be monitored at suitable scheduled intervals.
153. For products authorized for parametric release, a supporting presterilization bioburden monitoring programme for the filled product prior to initiating the sterilization cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilizing process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.
154. The sterility test applied to the finished product should only be regarded as the last in

a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.

155. The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

i. For products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples (for example, taken after critical interventions) should be considered based on risk.

ii. For products that have been heat sterilized in their final containers, samples taken should be representative of the worst-case locations (for example, the potentially coolest or slowest to heat part of each load).

iii. For products that have been lyophilized, samples should be taken from different lyophilization loads.

Note: Where the manufacturing process results in sub-batches (for example, for terminally sterilized products), then sterility samples from each sub- batch should be taken and a sterility test for each sub-batch performed. (Consideration should also be given to performing separate testing for the other parameters of the product.)

156. For some products, it may not be possible to obtain a sterility test result prior to release because the shelf-life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring or alternative test methods required to mitigate the identified risks should be assessed and documented.

157. Any substance or process (for example, vaporized hydrogen peroxide, ultraviolet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the outcome of the test.

158. Media used for product testing should be quality control tested according to the relevant pharmacopoeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative in-house isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.

159. Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification and release. A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with a short shelf-life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid or alternative methods.

160. Rapid and automated microbial methods should be validated.

## ANNEX II- MANUFACTURING BIOLOGICAL MEDICINAL PRODUCTS

### SCOPE

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex. Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA). The production techniques may involve:

a. Microbial cultures, excluding those resulting from r-DNA techniques.
b. Microbial and cell cultures, including those resulting from recombinant DNAor hybridoma techniques.
c. Extraction from biological tissues.
d. Propagation of live agents in embryos or animals.

### Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary. Unlike conventional medicinal products, which are reproduced using chemical and physical technique capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extractionof material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a great importance in the manufacture of biological medicinal products.

The special properties of biological medicinal products require careful consideration in any code of Good Manufacturing Practice and the development of this annex takes these points into account.

### Personnel

1. All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. Personnel should be given relevant information and training in hygiene and microbiology.
2. Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry,

chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.

3. The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Visitors should generally be excluded from production areas.
4. Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitoredby regular checks of immunological status or chest X-ray.
5. In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

## Premises and Equipment

6. The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the level of contamination of the starting materials and the risk to the finished product.
7. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.
8. In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.
9. Dedicated facilities should be used for the handling of Bacillus anthracis, of Clostridium botulinum and of Clostridium tetani until the inactivation process is accomplished.
10. Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.
11. Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.
12. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross- contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

13. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.
14. Air handling units should be specific to the processing area concerned and recirculationof air should not occur from areas handling live pathogenic organisms.
15. The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.
16. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.
17. Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilization. The use of "clean in place" and "sterilize in place" systems should be encouraged. Valves on fermentation vessels should be completely steam serializable. Air vent filters should be hydrophobic and validated for their scheduled life span.
18. Primary containment should be designed and tested to demonstrate freedom from leakage risk.
19. Effluents which may contain pathogenic microorganisms should be effectively decontaminated.
20. Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

## Animal Quarter and Care

21. Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). In addition, animals may also be used in the quality control of most sera and vaccines, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
22. Quarters for animals used in production and control of biological products should be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities. Where monkeys are used for the production or quality control of biological medicinal products, special consideration is required as laid down in the current WHO Requirements for Biological Substances.

## Documentation

23. Specifications for biological starting materials may need additional documentation on the source, origin, method of manufacture and controls applied particularly microbiological controls.
24. Specifications are routinely required for intermediate and bulk biological medicinal products.

## Production Starting Materials

25. The source, origin and suitability of starting materials should be clearly defined. Where the

necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

26. Where sterilisation of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).

## Seed Lot and Cell Bank System

27. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture of propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.
28. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the marketing authorisation dossier. Scaling up of the process should not change this fundamental relationship.
29. Seed lots and cell banks should be adequately characterised and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks should be established, stored and used in such a way as to minimise the risks of contamination or alteration.
30. Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.
31. Evidence of the stability and recovery of the seeds and banks should be documented. Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.
32. Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risks of total loss.
33. All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned.

## Operating Principles

34. The growth promoting properties of culture media should be demonstrated.
35. Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.
36. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.
37. If possible, media should be sterilised in situ. In-line sterilising filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where

possible.

38. Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.
39. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.
40. A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilised or sanitised between batches. The use of the same equipment at different stages of processing shouldbe discouraged. Acceptance criteria, life span and sanitization or sterilisation method of columns should be defined.

## Quality Control

41. In-process controls play an especially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product should be performed at an appropriate stage of production.
42. It may be necessary to retain samples of intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of a batch control.
43. Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.
44. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

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